American Academy of Allergy, Eleventh Annual Meeting, Statler Hotel, New York City, New York, February 7, 8, 9, 1955

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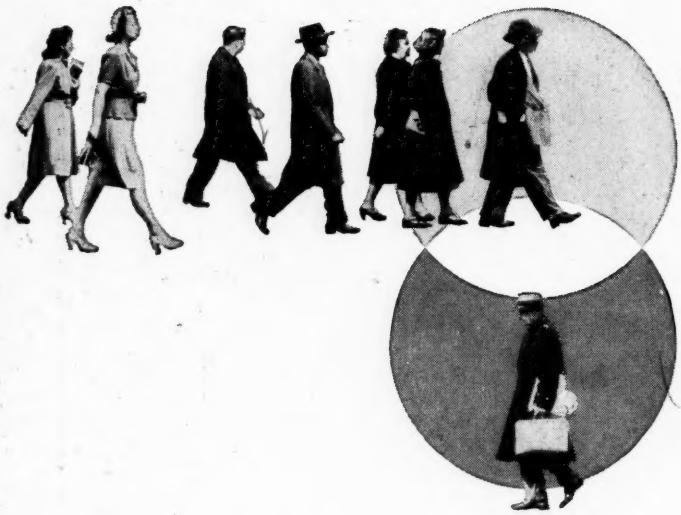

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Original Articles

STUDIES ON THE ANTIBODIES IN RABBIT ANTISERA RESPONSIBLE FOR SENSITIZATION OF HUMAN SKIN

II. CHARACTERISTICS OF ANTISERA TO EGG WHITE AND TO CONALBUMIN*

JOHN H. VAUGHAN, M.D.,** RICHMOND, VA., AND
ELVIN A. KABAT, PH.D., NEW YORK, N. Y.

IN A previous study[1] it was demonstrated that the ability of certain rabbit antisera to recrystallized egg albumin (Ea) to induce in human skin a wheal and erythema type of sensitivity was due to the presence in these sera of antibody to egg white constituents other than Ea. Evidence was presented to show that these antibodies resulted from trace impurities in the highly purified crysalline Ea used for immunization.

Previous studies by several groups of workers had already demonstrated that some, but not all, rabbit or guinea pig antisera to antigens such as egg white,[2] ragweed pollen,[3-6] horse serum,[7] or crystalline egg albumin[8] possessed the capacity passively to confer wheal and erythema sensitivity to human skin; no correlation between sensitizing capacity and precipitin content was noted. Sherman, Menzel, and Seebohm[8] also demonstrated that the original skin-sensitizing capacity of rabbit anti-Ea sera was retained after serial absorption with Ea so as to leave nonprecipitating anti-Ea in solution and inferred that nonprecipitating anti-Ea was skin sensitizing. In our recent study,[1] however, precipitating antibodies to several antigenic impurities were demonstrated in such preparations of nonprecipitating anti-Ea, and the sensitizing capacities were shown to be caused by antibodies as yet unidentified.

In the present report the characteristics of rabbit antisera to another purified egg white protein, crystalline conalbumin (Ca), and to whole egg white (EW) are described. It has been found that there are two distinct types of skin-sensitizing anti-Ca and anti-EW sera. These types correspond to similar types of skin-sensitizing anti-Ea sera previously described.[1] This general similarity in the skin-sensitizing propertes of ant-Ea, anti-Ca, and anti-EW sera is taken as a further indication that there are in EW a limited

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number of antigens capable of inducing in the rabbit the production of skin-sensitizing antibody and that these antigens are present as impurities in crystalline egg albumin and crystalline conalbumin.

MATERIALS AND METHODS

The materials, techniques, and procedures used in this study have been described in detail elsewhere.[1] The antigens used were recrystallized egg albumin, conalbumin, and lysozyme, and highly purified ovomucoid.* Whole egg white thoroughly dialyzed against saline was kept frozen and portions were thawed when needed.

All animals were immunized with intravenous alum-precipitated antigen,[1, 9] conalbumin being given as a series of 16 injections totaling 20 mg. per rabbit during the first month and 10 mg. per rabbit the second month. EW was given in a dosage of 20 mg. per rabbit during both months of immunization. Animals were bled on the fifth to seventh days after the last injection.

Analyses for antibody to the major antigenic component were performed by the quantitative precipitin technique,[9, 10] analyses for antibodies to the trace contaminants being carried out by the modification recently described.[1] Agar diffusion analyses,[11-13] as described in detail,[1] were used for estimating the number of antibodies in given antisera.

All skin tests were done on normal human subjects with negative allergic histories; 0.05 ml. of serum or serum dilution was used for sensitization and forty-eight hours later 0.01 to 0.02 ml. of antigen for eliciting the reactions, which were read at fifteen to twenty minutes.

RESULTS

In Table I are recorded the antibody analyses and skin test results on the sera from 9 rabbits immunized with conalbumin and 8 rabbits immunized with whole egg white. The preponderance of the antibody response in the anti-Ca sera was to Ca, but some anti-Ea was also regularly seen. In only 2 sera, $R224_4$ and $R226_4$, were significant amounts of anti-Lyso found and in none did anti-Ovo occur. The major antibody response in the anti-EW sera, on the other hand, was to Ea, lesser responses occurring to Ca, Ovo, and Lyso roughly paralleling the amounts of these antigens in EW.[14]

As had been previously observed in anti-Ea sera,[1, 8] there was no parallelism between the skin-sensitizing capacities of the various sera and their content of any of the precipitating antibodies measured. Furthermore, serum samples taken after only one month of immunization showed much lower skin-sensitizing capacity than those taken after two months. The sera in Table I are from the latter bleeding. As had also been noted for anti-Ea sera,[1] the present antisera could be divided into two distinct types on the basis of their patterns of response when the various purified antigens were used to elicit the reactions in sensitized skin sites. Thus, with 7 of the 9 anti-Ca sera, EW and Ca were approximately equivalent in their capacities to elicit the reactions, Ea being

*We are grateful to Dr. Robert C. Warner of New York University for the conalbumin, lysozyme, and ovomucoid.

TABLE I. ANTIBODY CONTENT AND SKIN-SENSITIZING CAPACITY OF RABBIT ANTISERA

	SERUM DESIGNATION	ANTIBODY CONTENTS				REACTIONS ELICITED IN SKIN SITES SENSITIZED WITH 0.05 ML. OF SERUM AND TESTED WITH 10 μG N OF				
		ANTI-EA	ANTI-CA	ANTI-OVO	ANTI-LYSO	EW	EA	CA	OVO	LYSO*
		μg sp. ppt.N/ml.	μg AbN/ml.	μg sp. ppt.N/ml.	μg sp. ppt.N/ml.					
				Anti-Ca Sera						
	$R218_4$	9	262	0	0	++±	±	++±	–	
	$R219_4$	16	377	4†	0	++	±	+	–	
	$R220_4$	17	328	0	0	±	–	±	±	
Type I	$R223_4$	16	468	2†	0	++	±	+++	–	
	$R224_4$	20	557	2†	12	+±	±	++	+	
	$R225_4$	13	157	0	3†	±	–	±	–	
	$R227_4$	10	412	0	0	±	–	±	–	–
Type II	$R221_4$	11	66	0	4†	++±	++	±	–	
	$R226_4$	20	536	2†	25	++	+	+	±	
		μg AbN/ml.	μg AbN/ml.	μg sp. ppt.N/ml.	μg sp. ppt.N/ml.					
				Anti-EW sera						
Type I	$R236_4$	0	0	0	0	++	+	++	+	–
	$R238_4$	218	31	35‡	0	++	+	++	+	
	$R233_4$	50	28§	6‡	0	++	±	±	–	
Type II	$R234_4$	792	45	40	0	++	+	±	–	–
	$R240_4$	66	52	26	20	++	++	+	–	
	$R241_4$	916	68	56	13	+	±	–	–	
	$R242_4$	926	81	46	25	+	±	–	–	
	$R243_4$	36	38	17	0	–	–	–	–	–

*Lyso used only in 1 μg N quantity, as 10 μg N produced nonspecific irritation.
†Values not significant.
‡AbN.
§Spec. ppt. N.

distinctly less potent (Type I). With the other 2 sera, EW was the most reactive antigen, Ea being next, and Ca relatively unreactive (Type II). Reactions with Ovo were inconstant. Lysozyme could not be adequately evaluated, as in the high concentration (1.0 mg. N/ml.) of antigen required to elicit reactions with these relatively weak sera lysozyme was a primary irritant, giving wheal and erythema responses in control sites as well as in sensitized sites. When used at a concentration of 0.1 mg. N/ml., it gave no reactions in either sensitized or control sites. Among the 8 anti-EW sera, there were 2 of Type I and 5 of Type II. One serum failed to develop a sensitizing capacity.

The striking difference in the incidence of the 2 types of sensitizing sera among the anti-Ca and anti-EW groups is interesting. Though a larger number of such sera would have to be studied to establish definitely the statistical significance of this difference, the finding seems logical and consistent with the assumption that crytalline Ca is contaminated to a relatively greater degree with the EW antigen reacting with the skin-sensitizing antibody of the Type I sera than with the antigen specific for the skin-sensitizing antibody in the Type II sera, as indicated by the relative potencies of Ca in eliciting reactions with the two types of sera.

Although there was no apparent parallelism between the sensitizing capacities of the anti-Ca sera and their content of anti-ca and although it was shown by absorption studies[1] that neither precipitating nor nonprecipitating anti-Ca was responsible for the passive transfer capacity of anti-Ea sera, it seemed wise to repeat such studies in these anti-Ca sera, in which anti-Ca was the major antibody. Since the sensitizing capacities of these sera were relatively weak, it was necessary to study partially as well as completely absorbed sera to obtain the critical data. The results are tabulated in Table II, from

TABLE II. EFFECT OF ABSORPTION OF ANTICONALBUMIN SERA WITH CONALBUMIN

SERUM DESIGNATION	Ca N ADDED TO 1.0 ML. SERUM	TOTAL N PPTD.	ANTI-Ca N PPTD.	SUPERNATANT TEST FOR EXCESS		REACTION ELICITED BY 10 μG EW PROT. N IN SITES SENSITIZED WITH 0.05 ML. OF SUPERNATANT IN SKIN OF	
				AB	AG	J. M.	P. A.
$R221_4$	μG	μG	μG.				
	0	0	0			+±	++
	4.6	37	33	++	0	+±	++
	7.0	66	59	+	0	+	+±
	10.0	81	71	0	0	+	+±
	14	105	101	0	+	±	+±
	18	109	91	0	+	±	+±
$R223_4$	0	0	0			+	+
	23	364	341	+++	0	±	+
	46	514	468	tr	0	−	+
	69	592	523	0	0	−	+
	92	622	530	0	+	−	+
	115	636	521	0	++	−	+

which it can be seen that the disappearance of passive transfer capacity in the two sera did not coincide with the point at which anti-Ca was completely absorbed. The variability of the reactivity of the sera in different recipients is consistent with similar previous findings by the present authors,[1] as well as others using antisera from laboratory animals[2-8] or naturally sensitive patients.[15]

When anti-EW sera of both types were absorbed with increasing amounts of EW (Table III), it was clear that the amount of EW required for neutralization of skin-sensitizing ability was primarily related to the potency of the original serum and was definitely greater than the amount necessary for neutralization of all anti-Ea, anti-Ca, anti-Ovo, and anti-Lyso in the sera. For serum $R241_4$, for instance, the latter was calculated to be 50 μg EW prot. N/0.5 ml.[16] whereas more than 163 μg EW prot. N/0.5 ml. was required to neutralize the passive transfer activity (Table III) for $R241_4$. For serum $R236_4$, the figures were 10 μg N and $>$ 4,090 μg N, respectively. Furthermore, separate preliminary absorption of these antibodies with purified preparations of Ea, Ca, Ovo, and Lyso from sera $R234_4$ and $R238_4$ reduced sensitizing capacity only slightly and in proportion to what might be expected on the basis of impurities in the absorbing antigens.

TABLE III. EFFECT OF ADDITION OF INCREASING AMOUNTS OF EGG WHITE TO ANTI-EGG WHITE SERA

SERUM DESIGNATION	EW PROT. N ADDED TO 0.5 ML. SERUM	SPECIFIC PPT. N	REACTION ELICITED BY 10 μG EW PROT. N IN SITES SENSITIZED WITH 0.05 ML. OF SUPERNATANT (SERUM 1:3)
	μG	μG	
$R241_4$	0	0	+±
	163	341	±
	409	110	−
	818	40	−
	1,636	40	−
	4,090	21	−
$R236_4$	0	0	++++
	818	21	+++±
	2,454	22	++
	4,090	18	++
$R234_4$			+±
$R234_4A$*	0	0	+
	409	24	
	818	24	+
	1,227	22	
$R238_4$			++
$R238_4A$*	0	0	+±
	163	9	+
	409	21	+
	818	27	±
	1,636	28	−
	4,090	23	−

*Sera absorbed successively with Ea, Ca, Ovo, and Lyso.

DISCUSSION

The failure of rabbit anti-Ca or anti-EW sera to manifest any characteristic feature that would allow the differentiation of their sensitizing properties from those of anti-Ea sera may be taken as further evidence in support of the previously expressed hypothesis[1] that there are in EW a limited number of antigens, possibly only two, that are capable of eliciting skin-sensitizing antibody in the rabbit. These antigens appear to contaminate crystalline preparations of both Ea and Ca, and they are minor and otherwise undefined components of EW. Quantitatively the great preponderance of antibodies in these anti-Ca and anti-EW sera is antibody to the four major EW constituents, Ea, Ca, Ovo, and Lyso,[14] but none of these major rabbit antibodies appear to have skin sensitizing capacity in human beings[1] (Table III).

The concept that only certain antigens may have significance in human skin sensitivity is supported by clinical experience,[17] and in recent years several studies on the fractionation of various allergen extracts have provided data to indicate that, with a given allergen extract, only some of the antigens present can react in sensitized skin.[18-21] The recent report by Miller and Campbell[22] that there are in EW "perhaps materials not yet described" to which egg-sensitive patients may react also is significant, and one may hypothesize that the activities of the purified protein preparations used by these workers, just as those in the present study, were due not to the major antigens but to materials present as contaminants. There are as yet no definitive data,

however, to tell whether or not the EW antigens productive of skin-sensitizing antibody in the rabbit are the same as those producing skin-sensitizing antibody in man. Likewise there is no reason to believe that the active ingredient of any particular allergenic mixture is necessarily a minor constituent.

No information is provided by this study on the question of the precipitability of skin-sensitizing antibody. Although the medical literature is replete with the idea that skin-sensitizing antibody is nonprecipitating and often implies that this behavior in some mysterious way confers upon the antibody the capacity to sensitize skin, there is as yet no convincing evidence on this point. Defined immunochemically, nonprecipitating antibody is antibody which by itself will not precipitate with antigen, but which may be carried down in aggregates of antigen with precipitating antibody to the corresponding antigen. That antiragweed skin-sensitizing antibody, for instance, has not been precipitated by ragweed extract cannot be taken as proof that this antibody is nonprecipitating, for it is clear that if either the antigen or the antibody is present in sufficiently low concentration it is impossible to form visible precipitates for quantitative reasons alone. In the same fashion, it would be improper to consider a given complement-fixing antibody to be nonprecipitating simply because no antigen-antiserum combination had been found which would produce a precipitate, though such failure of precipitation is frequent in human convalescent sera with high complement fixation titers. Indeed, human nonprecipitating diphtheria antitoxin has been found to fix complement much more poorly per unit of antitoxin than its precipitating counterpart.[23] Waksman's recent assertion[24] that rabbit anti-Ea sera contain a nonprecipitating skin-sensitizing antibody makes this very error, by the apparent assumption that because a precipitating skin-sensitizing antibody could not be demonstrated, the antibody was nonprecipitating.

The only report in the literature which clearly demonstrates the presence of a truly nonprecipitating antibody in a skin-sensitizing serum is that of Kuhns and Pappenheimer[23] who used a diphtheria toxoid-antitoxin system in man and believed that the nonprecipitating antitoxin was the skin sensitizing antibody. However, a more recent report by Kuhns[25] on a rather striking separation of the two types of antibody by alcohol fractionation adds further to doubts already expressed by us[1] as to the identity of the nonprecipitating and skin-sensitizing antibodies. Kuhns'[26] interpretation that this apparent separation was an artifact probably due to antibody denaturation during the separation procedures requires independent experimental substantiation.

In contradistinction to the prevalent concept that antibody formed in a given individual to a given antigen may or may not be skin sensitizing in accordance with certain characteristics of the antibody made by that individual, the present findings emphasize the importance of the antigen as a major determinant. It is not known why certain antigens are productive of skin-sensitizing antibody while others apparently are not.

SUMMARY AND CONCLUSIONS

The skin-sensitizing capacities of rabbit antisera to egg white and to conalbumin are identical in their essential features with those previously shown for antisera to egg albumin. Two types of antisera are seen within each group, apparently on the basis of two different skin-sensitizing antibodies not corresponding to anti-Ea, anti-Ca, anti-Ovo, or anti-Lyso. The limited number of egg white antigens capable of eliciting skin-sensitizing antibody in the rabbit is also pointed out, and the presence of these antigens as impurities in even the highly purified preparations of the egg white proteins used in this study is indicated.

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PREVENTION OF REACTIONS IN INTRAVENOUS UROGRAPHY

S. William Simon, M.D.,* Henry I. Berman, M.D.,** and
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IN DISCUSSING a method to lessen penicillin reactions, one of us (S.W.S.) suggested that antihistaminic drugs could be combined with other preparations which occasionally cause reactions and thereby abolish or definitely reduce their incidence.[12] About the same time Getzoff[3] introduced his method of reducing reactions to intravenous Diodrast (the diethanolamine salt of 3, 5—diiodo—4—pyridone—N—acetic acid) by giving the patient orally 50-200 mg. of Pyribenzamine (N, N—dimethyl—N[1] benzyl—N[1] (Alpha-pyridyl)—ethylene diamine). In 1951 Olsson[8] added 20 mg. of Benadryl (2—[Benzhydryloxy]—N, N—dimethylethylamine Hydrochloride) to each 20 ml. of Diodrast solution, and in 1953 Moore and Sanders[5] tried 20 mg. of Benadryl and later 6 mg. Thenfadil (2—[(2—Dimethylaminoethyl)—3—thenylamino] pyridine) with each 30 ml. of Diodrast solution.

The dangers of injecting intravenous contrast materials are real, and at least twelve deaths had been reported in the literature up to 1949. The "milder" reactions consist of chills, flush, arm pain, nausea, vomiting, and urticaria. Of these "milder" reactions, nausea, vomiting, and urticaria are considered allergic and the others as vasomotor phenomena. The more severe reactions consist of edema of the eyelids, laryngospasm, bronchospasm (asthma), vertigo, pallor of the skin, syncope, cyanosis, and other evidences of shock. Of these, edema of the eyelids, laryngospasm, bronchospasm, vertigo, and shock may be considered allergic or anaphylactoid. It is beyond the scope of this paper to consider any but the allergic reactions which should be reduced by antihistamines. Vasomotor reactions will not be noted as they are unaffected.

All drugs used as contrast media in urography are iodide salts and probably the iodine acts as a haptene although the speed of some reactions in extremely sensitive patients causes one to wonder. Sherman[10, 11] doubts the value of scratch or patch tests to nonprotein drugs. Alyea and Haines[1] reported four times as many reactions in patients with previously noted positive intradermal tests as in those with negative. Our experiences with the intradermal and eye sensitivity tests have only served to emphasize their futility and unreliability. We do agree with these authors, however, that patients with a history of allergy are much more likely to react to the contrast media than those without such a history.

Many papers have appeared comparing the percentage and severity of reactions using the various drugs. As we are not extolling the efficacy or

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paucity of reactions of any of the drugs used as contrast media, we have added together the figures for each drug in the production of side reactions and sensitivity symptoms. To arrive at the percentage of patients exhibiting these various signs, the figures of several authors are given for each symptom, and then these are averaged to arrive at a control percentage (Table I). It is noted that in almost 5,700 patients given contrast media over 17 per cent developed some type of allergic reaction to the drug used.

The comparative figures as reported by Ollson and Moore and Sanders adding an antihistamine to the contrast drug are given in Table II. In 726 patients given Diodrast and Benadryl or Thenfadil, the average reaction rate was 9.7 per cent.

Our series of 530 patients was composed of both outpatients and those in the hospital. With Diodrast the 35 per cent solution was used, 20 ml. being given to patients under 150 pounds, 25 ml. from 150 to 175 pounds, and 30 ml. if over 175 pounds. The Chlor-Trimeton* (1—para-chlorophenyl—1—[2—pyridyl]—3—dimethylaminopropane) maleate solution, which contained 5 mg. of the drug in each 2.5 ml., was withdrawn from 10 ml. rubber-capped vials and mixed in the syringe with the Diodrast; 5 mg. were used with 20 ml. of Diodrast and 6 mg. with 25 or 30 ml.

TABLE I. PERCENTAGE OF REACTION SYMPTOMS (CONTROLS)

NAME	NO. OF PATIENTS	HISTORY OF ALLERGY	NAUSEA	VOMITING	URTICARIA	DIZZINESS	SNEEZING, ASTHMA, WHEEZING	UNCONSCIOUSNESS	ALL SYMPTOMS	CONTRAST MEDIA USED
Nesbit and Lapides[6]	1,281		10.7	3.5	2.03	1.4	0.13		17.8	Urokon, Diodrast and Neo-Iopax
Robbins, Colby, Sosman and Eyler[9]	2,952	8.5	9.0	4.7	0.65		0.75	0.03	15.1	Urokon and Diodrast
Nesbit and Nesbit[7]	1,000		12.0	4.0	1.0	0.0			17.0	Urokon
Olsson[8]	500		15.0	4.0	1.0		3.8	0.2	24.0	Diodrast
Moore and Sanders[5]	111		23.4	5.4	9.9		6.3		45.0	Diodrast
Total or Average	5,694	8.5	10.6	4.2	1.2	0.8	1.0	0.1	17.3	

Likewise, in those patients receiving 50 per cent Neo-Iopax (the disodium salt of N—methyl—3, 5—diiodo-chelidamic acid) the amount of solution used and of antihistamine added were the same as with Diodrast.

*Chlor-Trimeton used in this series was furnished through the courtesy of the Schering Corporation, Bloomfield, N. J.

TABLE II. PERCENTAGE OF REACTION SYMPTOMS WITH ANTIHISTAMINE ADDED (FROM LITERATURE)

AUTHORS AND DRUG USED	NO. OF PATIENTS	NAUSEA	VOMITING	URTICARIA	RESPIRATORY SYMPTOMS	ALL SYMPTOMS	CONTRAST MEDIUM USED
Olsson (Benadryl)[8]	500	4.6	0.4	0.8	0.4	6.0	Diodrast
Moore and Sanders[5] (Benadryl)	110	16.3	1.8	3.6	2.7	24.4	Diodrast
Moore and Sanders[5] (Thenfadil)	116	12.1		0.9	0.9	13.9	Diodrast
Total or Average	726	7.3	0.54	1.2	1.3	9.7	

Those patients who were given 30 per cent Urokon Sodium (the sodium salt of 3 acetylamino—2, 4, 6—triodobenzoic acid) all received 25 ml. mixed with 6 mg. of Chlor-Trimeton regardless of weight or history of allergy. It should be added, however, that the patients in the Diodrast or Neo-Iopax series who had either a history of allergy or previous reaction to iodides or contrast media usually were given 10 mg. of Chlor-Trimeton.

The results are noted in Table III which in summary gave an over-all reaction rate of 7.1 per cent. However, each type of reaction is considered separately, and if one patient developed nausea, vomiting and urticaria, the three symptoms were added to the total.

All reactions were mild and generally subsided quickly without added medication. However, epinephrine was always kept handy and 0.5 ml. was given on three occasions and intravenous Benadryl on two, in each case after the use of Urokon which also produced all of the delayed reactions. As the patients receiving Urokon were without exception outpatients while all of the others were hospitalized, this, too, must be taken into consideration.

TABLE III. RESULTS WITH CHLOR-TRIMETON ADDED TO CONTRAST MEDIA

DRUG	NO. OF PATIENTS	HISTORY OF ALLERGY	NAUSEA	VOMITING	URTICARIA	SNEEZING	ASTHMA, WHEEZING	UNCONSCIOUSNESS	DELAYED REACTION
Urokon 30 per cent	85	3	5	2	0	0	2	0	12
Neo-Iopax 50 per cent	303	19	8	2	0	0	1	0	0
Diodrast 35 per cent	142	17	12	0	2	3	1	0	0
Totals	530	39	25	4	2	3	4	0	12
Percentage of total		7.3	4.7	0.7	0.3	0.6	0.7	0	2.2

7.1 per cent of patients had reaction.

Case histories of three patients each of whom had a peculiar problem follow:

CASE 1.—A 42-year-old paraplegic physician gave a history of a severe reaction to two previous attempts at intravenous urography. He did not know which drugs were used at those times but with each developed much apprehension, nausea, vomiting, and unconsciousness. The skin and eye tests previous to injection were negative. Due to these previous reactions we added 5 ml. or 10 mg. of Chlor-Trimeton maleate to 20 ml. of Diodrast. The patient experienced transient mild arm pain and a slight face flush lasting less

than thirty seconds but no other reaction of any type. Three months later several needles were placed in his back to locate ganglia for paravertebral block and some Diodrast solution was introduced with each needle in order to locate them by x-ray. A very small amount of the contrast medium was used, but the patient developed severe nausea, vomiting, and mental confusion immediately following the injection and the procedure had to be stopped. Later, the Diodrast was used in the same way but with Chlor-Trimeton added and the study was completed without difficulty. A repeat intravenous pyelogram was made some months later using Neo-Iopax and Chlor-Trimeton. The patient experienced no untoward symptoms.

CASE 2.—A 24-year-old white man was hospitalized for the treatment of a ureteral calculus and pyelonephritis. An intravenous urographic study was attempted using Diodrast following a negative dermal test. After about 5 ml. had been injected the patient complained of burning of his chest, arms, and legs, and shortly thereafter developed urticaria on these parts. There was no previous history of allergy. A urographic study was completed later by using Neo-Iopax to which 5 mg. of Chlor-Trimeton had been added.

CASE 3.—A 60-year-old white man with a long history of chronic bronchial asthma was given the intravenous injection of Neo-Iopax with 5 mg. of Chlor-Trimeton added without producing any reaction or of aggravating the pre-existing bronchial asthma.

DISCUSSION

It is obvious from a comparison of the figures given in the studies of various authors that wide discrepancy exists. Where both Olsson and Moore and Sanders used Benadryl with Diodrast, the Americans Moore and Sanders had four times as many reactions as the Swedes. Perhaps the latter are hardier, but the more likely explanation lies in the way the injections are given and the interpretation of the reactions. In our experience, the following factors will reduce vasomotor reactions and possibly nausea and vomiting: (1) Warm solution to body temperature before injecting. (2) Inject 1 ml. of solution slowly, then wait approximately one minute to determine individual tolerance following which the remainder of the solution is injected quite rapidly. (3) Use smallest needle consistent with intravenous injection—probably 22 gauge.

We have made our comparisons using the symptoms in the control series which are least controversial and most likely to be on an allergic basis. It is questionable if nausea and vomiting are allergic symptoms, but as they are reduced in all series by the use of antihistamines, they are included. Vasomotor symptoms such as chills, fever, flushing, arm pain, and dizziness are not included because they are caused many times by merely drawing blood and apparently are not reduced by using the antihistamines. The respiratory symptoms consist of sneezing, laryngospasm, bronchospasm, or asthma, and it is felt that these are definitely due to allergy. Unconsciousness, when it occurs, is a severe, generalized, anaphylactoid reaction.

Delayed reactions are harder to explain. All of ours took place in outpatients and were possibly aggravated by apprehension. The formation of a conjugated antigen takes just as long in the hospital as outside.

In spite of Getzoff's[3] good results using premedication with oral antihistamines, several authors feel that this procedure does not materially reduce reactions.[2, 6]

One of us (S.W.S.) has devoted much time to the prevention of reactions from penicillin by adding an antihistamine to the diluent. The opinion is expressed that there is an optimum dose for each antihistaminic drug, somewhere below the toxic dose, which will protect the most sensitive patient.[13, 14] However, some patients may either have or develop a refractoriness to certain antihistamines[4] so the ideal result of no reactions will never be reached. We are continuing our studies but with increased dose of Chlor-Trimeton (10 mg.). This amount was very effective in materially reducing reactions in blood transfusions.[15]

SUMMARY

A total of 530 intravenous urographic examinations were made using various contrast media to which were added from 5 to 10 mg. of Chlor-Trimeton. While vasomotor reactions were not influenced, the allergic reactions of nausea, vomiting, urticaria, sneezing, wheezing, and syncope were reduced from a control level of 17.3 per cent to 7.1 per cent.

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ANTIHISTAMINE AND ANTICONGESTANT SOLUTIONS APPLIED TO NASAL MUCOUS MEMBRANES

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THE Medical Department of the United States Air Force is aware that many members of the Air Service use antihistamine and anticongestant solutions in the nose to control the symptoms of the common cold and to relieve the congestion of the mucous membrane of the nasopharynx. These conditions frequently accompany or follow flight. Precise information is not available as to whether the infrequent or frequent use of these drugs endangers personnel.

At the request of the Air Research and Development Command the present study was undertaken to: (1) establish a reliable estimate of the effectiveness of antihistamine and anticongestant solutions in their relative order of merit; (2) determine the extent of side reactions, local and systemic, of each compound for varying case types and for different lengths of usage; (3) determine whether the use of such medication, either on a short or a prolonged basis, should be considered proper reason for grounding flying personnel, and (4) determine the length of time following use of each compound that a flyer should be prevented from going aloft.

SELECTION OF PATIENT GROUPS

Ambulatory groups of patients were chosen at random and were referred from the Allergy Clinic of the Johns Hopkins Hospital to the Department of Otolaryngology. No special selection of patients was made because many of the patients had had routine treatment to prevent late summer hay fever. They were free of any nasal or constitutional symptoms at the time of the present study. Some were suffering from mild to severe symptoms of hay fever caused by the pollen of trees and grasses; others were suffering from bronchial asthma and urticaria, or were under treatment to prevent the common cold. Patients whose nasal membranes were normal, as well as those whose membranes were congested by specific sensitivity, participated in this investigation.

METHOD OF STUDY

Each patient was questioned concerning allergic manifestations of the respiratory tract. The number of winter colds was recorded. If there was a history of sinus disease, pollen hay fever, allergic rhinitis, or bronchial asthma, this information was noted.

From the Allergy Clinic of the Medical Department (Dr. Gay) and from the Otolaryngological Clinic of the Surgical Department of the Johns Hopkins University and Hospital (Dr. Polvogt).

This investigation was carried out under contract with the Air Research and Development Command.

The drugs used in this study were supplied by the following companies: Ciba Pharmaceutical Products, Inc.; Eli Lilly and Company; Parke, Davis & Company; Schering Corporation; Winthrop-Stearns, Inc.; and Wyeth, Incorporated.

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Careful pulse records and blood pressure readings were made in each patient immediately before any drug was applied to the nasal passages. When the nose was examined, the character of the mucous membranes, the amount of breathing space, and the presence of discharge and of infection were especially noted.

The groups of patients were examined and treated each week. The nose was packed with cotton pledgets that had been soaked in a solution of the drug. After the packs had remained in place for fifteen minutes they were removed, and the nose was re-examined. The character of the mucous membranes was observed; the amount of shrinkage that had taken place was recorded, and an experienced nurse looked for any evidence of nervousness, drowsiness, gastric distress, or miscellaneous complaints which might have accompanied or followed the treatment. After removal of the packs, the circulation was checked, and pulse and blood pressure readings were recorded. The patients of each group were given the same therapeutic agent to use at home, two or three drops into each nostril every two to four hours during the day for seven days. On the third and fifth day of treatment, each patient was visited by a trained nurse who observed and questioned him concerning nervousness, drowsiness, gastric distress, and other miscellaneous complaints. On the seventh day each patient returned to the clinic for further observation of the nose. The final impression of the effect of the drug on the mucous membranes and on the general condition of the patient was recorded.

DRUGS EMPLOYED

Six well-known antihistamine and two anticongestant solutions were selected for this study. A single drug was used each week to avoid confusion. Patients were not questioned as to which drug was most beneficial. All records of drug action are based entirely on professional observation. For a control group, 28 patients were treated with normal saline solution in the same manner as were those who received the specific drugs. Patients were not aware that the "medication" was an inactive solution.

The following drugs were used: (1) Chlorprophenpyridamine maleate (Chlor-Trimeton maleate), 0.1 per cent; (2) Histadyl, 0.5 per cent; (3) phenylephrine hydrochloride (Neo-Synephrine hydrochloride), 0.25 per cent; (4) Bena-Fedrin, a mixture containing Diphenhydramine Hydrochloride (Benadryl hydrochloride), 0.1 per cent ephedrine; 1.0 per cent; and chlorobutanol (Chloretine) 0.5 per cent; in a solution containing menthol and dextrose; (5) mixture containing phenylephrine hydrochloride, 0.25 per cent and Thenfadil, 0.1 per cent; (6) Naphazoline hydrochloride (Privine hydrochloride), 0.5 per cent; (7) Tripelennamine hydrochloride (Pyribenzamine hydrochloride), 0.5 per cent; (8) mixture containing Phenergan, 0.1 per cent and mephentermine sulfate (Wyamine sulfate), 0.5 per cent in isotonic dextrose solution; (9) normal saline solution, 0.85 per cent.

Chlorprophenpyridamine Maleate.—Of 15 patients who were treated with this drug, the mucous membranes of 7 (46.6 per cent) shrank satisfactorily.

No adverse constitutional reactions occurred during the observation period of two hours. Although shrinkage was present in the majority during the seven days of subsequent treatment, 33.3 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure in 2 patients (13.3 per cent) was increased during the period of observation.

Histadyl.—Of 21 patients who were treated with this drug the mucous membranes of 9 (42.8 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during two hours of observation. Although shrinkage was present in the majority during the seven days of subsequent treatment, 33.3 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in 3 patients (14.2 per cent) during the period of observation.

Phenylephrine Hpdrochloride.—Of 30 patients who were treated with this drug, the mucous membrane of 29 (96.6 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during the observation period of two hours. Although shrinkage was present in the majority during the seven days of subsequent treatment, 46.6 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in 8 patients (26.6 per cent) during the period of observation.

Mixture Containing Phenylephrine Hydrochloride and Thenfadil.—Of 25 patients who were treated with this drug, the mucous membranes of 23 (92.2 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during the two hours of observation. Although shrinkage was present in the majority during the seven days of subsequent treatment, 60 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in four patients (16 per cent) during the period of observation.

TABLE I. NUMBER AND PERCENTAGE OF INDIVIDUALS WITH MUCOUS MEMBRANE SHRINKAGE, AND PERCENTAGE OF SUBJECTS WITH SYSTEMIC REACTIONS WITHIN SEVEN DAYS OF TREATMENT

DRUG	NUMBER OF CASES	MUCOUS MEMBRANE SHRINKAGE NO.	MUCOUS MEMBRANE SHRINKAGE %	PER CENT OF SUBJECTS WITH SYSTEMIC REACTIONS WITHIN 7 DAYS: ANY SYSTEMIC REACTION	DROWSINESS	NERVOUSNESS	DIZZINESS	HEADACHE	GASTRIC DISTRESS	MISCELLANEOUS
Chlorprophenpyridamine	15	7	46.6	33.3	20.0	13.3	6.7	6.7	0.0	0.0
Histadyl	21	9	42.8	33.3	28.6	14.3	14.3	4.8	23.8	9.5
Phenylephrine	30	29	96.6	46.7	13.3	26.7	3.3	3.3	6.7	13.3
Phenylephrine and Thenfadil	25	23	92.0	60.0	36.0	28.0	0.0	0.0	16.0	0.0
Naphazoline	35	34	97.1	60.0	45.7	28.6	0.0	0.0	0.0	2.9
Tripelennamine	27	27	100.0	40.7	33.3	29.6	0.0	0.0	3.7	0.0
Phenergan and mephentermine	12	11	91.6	33.3	16.7	25.0	0.0	0.0	8.3	0.0
Bena-Fedrin	12	12	100.0	58.3	50.0	50.0	0.0	0.0	8.3	0.0
Saline Control Group	28	7	25.0	7.1	3.6	3.6	0.0	0.0	3.6	0.0

Naphazoline Hydrochloride.—Of 35 patients who were treated with this drug, the mucous membranes of 34 (97.1 per cent) shrank satisfactorily. No

adverse constitutional reactions occurred during the observation period of two hours. Although shrinkage was present in the majority during the seven days of subsequent treatment, 60 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in 13 patients (37.1 per cent) during the period of observation.

Tripelennamine Hydrochloride.—Of 27 patients who were treated with this drug, the mucous membranes of all (100 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during the two hours of observation. Although shrinkage was present in all of the patients, 40.7 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in 4 patients (14.8 per cent) during the period of observation.

Mixture Containing Phenergan and Mephentermine Sulphate.—Of 12 patients who were treated with this drug, the mucous membranes of 11 (91.6 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during the observation period of two hours. Although shrinkage was present in the majority during the seven days of subsequent treatment, 33.3 per cent of those patients who used the drug every few hours manifested disturbing symptoms. Systolic blood pressure was increased in three patients (25 per cent) during the period of observation.

Normal Saline Solution.—To determine the effect of any fluid application on the mucous membranes, a control agent is necessary; normal saline solution was selected. Of 28 patients who were treated with this solution, the mucous membranes of 7 (25 per cent) shrank just as much as the membranes of those who were treated with antihistamine drugs. No adverse constitutional reactions occurred during the two hours of observation. In contrast with those patients treated with drugs, only 2 patients (7.1 per cent) manifested any disturbing symptoms.

Bena-Fedrin.—Of 12 patients who were treated with this drug, the mucous membranes of 8 (66.6 per cent) shrank satisfactorily. No adverse constitutional reactions occurred during the observation period of two hours. Although shrinkage was present in the majority during the seven days of subsequent treatment, 58.3 per cent of those patients who used the drug every few hours manifested disturbing symptoms.

DISCUSSION

The accumulated data reveal factual information concerning nasal shrinkage agents that physicians, and more recently the United States Air Force, have been seeking.

The drugs that were studied are most effective as shrinkage agents. Histadyl and Chlorprophenpyridamine maleate were the least effective of these eight drugs (less than 50 per cent); however, these two drugs caused no circulatory reaction, and the percentage of disturbing reactions (33.3 per cent) was lower than that of five other drugs. These five drugs (phenylephrine hydrochloride, mixture containing phenylephrine hydrochloride and Thenfadil,

naphazoline hydrochloride, tripelennamine hydrochloride, and Bena-Fedrin) were effective in more than 90 per cent of the patients who received treatment. Of those treated with these drugs, 40 to 60 per cent were disturbed by reactions that contraindicated prolonged use. The mixture containing Phenergan and mephentermine sulfate, the exception among the eight drugs, was effective as a shrinkage agent in more than 90 per cent of the subjects; furthermore, only 33.3 per cent of the patients were disturbed by reactions that contraindicated prolonged use.

Of the 205 patients participating in this investigation, 28 persons used as controls were treated with normal saline solution. Seven controls (25 per cent) exhibited shrinkage of the mucous membrane, but only 2 (7.1 per cent) were disturbed by drowsiness and nervousness. Of the remaining 177 patients, 148 (83.6 per cent) responded satisfactorily. None of the 177 patients showed any immediate reactions to local applications with cotton pledgets saturated with any of the drugs. Thirty-seven (20.9 per cent) developed circulatory reactions characterized by elevation of systolic blood pressure.

The reactions which followed prolonged usage—drowsiness, nervousness, dizziness, and gastric distress (especially the first two)—were numerous. The drowsy patient invariably complained of extreme nervousness. Gastric distress and dizziness were not frequent complaints. Ninety-one (51.4 per cent) complained of drowsiness and nervousness to such a degree that continued use of any of these drugs was contraindicated. Compared with the control group treated with normal saline solution (51.4 per cent as opposed to 7.5 per cent), the contrast figures are most significant.

CONCLUSION

The survey revealed that the immediate reactions, both local and constitutional, did not contraindicate the use of any of the eight drugs that were studied. The action was beneficial; congested mucous membranes shrank noticeably after application of a solution. The constitutional reactions which followed continued usage were so disturbing that the patient's judgment might be inaccurate and his reflex reactions sluggish. Therefore, prolonged usage should be considered proper basis for grounding flying personnel. Only by future study of the defects of vision and coordination that might accompany drowsiness and nervousness can one arrive at a scientific opinion as to the length of time a flyer should be grounded after he has discontinued the use of these antihistamine and anticongestant solutions in the nasal passages. However, long experience with antihistamine drugs taken orally by many patients has accumulated sufficient evidence to state that constitutional reactions completely subside within forty-eight hours after cessation of the drug.

A STUDY ON PROTEIN NITROGEN AND TOTAL NITROGEN VALUES OF VARIOUS FOOD EXTRACTS

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IN ACCORDANCE with the standardization procedure proposed by Cooke and Stull[1, 2] for pollen extracts, all pollen and inhalant extracts prepared in this laboratory are standardized on their proetin nitrogen basis.* In the case of food extracts, it was formerly believed that protein represented as a rule at least 90 per cent of the total nitrogen value and, therefore, the standardization of food extracts was practiced in previous years on the basis of total nitrogen, because of the greater convenience of this procedure. Doubts as to the validity of this belief arose; when 143 food extracts were analyzed for both protein nitrogen and total nitrogen, these doubts were confirmed.

The results of these 143 analyses are included in a mimeographed list for the benefit of laboratories that may desire to perform protein nitrogen determinations in standardizing food extracts.†

Although the protein nitrogen values of some 30 extracts fell within the range of 90 per cent of their total nitrogen values,‡ this was not the case in the vast majority, where the ratios of these two values were found in a lower range, even as low as 17.9 per cent (rhubarb). Moreover, in some instances, these ratios varied considerably in different preparations of the same extract. Examples in this regard together with some other representative results are given in Table I. Considering such significant variations, which do not allow any constant correlation of the two nitrogen values, it seems quite possible that even other extracts, which in this study appeared to adhere to the "rule of 90 per cent," would fail to do so with any degree of regularity.

CONCLUSION

1. No regular correlation exists between protein nitrogen and total nitrogen values for food extracts and considerable variations in the ratios of these values may even occur in different preparations of the same extract.

2. Food extracts should be standardized on a protein nitrogen basis in the same manner as pollen and inhalant extracts.

From The Institute of Allergy, The Roosevelt Hospital, New York City.

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*The term "protein nitrogen" signifies the nitrogen present in the precipitate obtained from an extract sample with the aid of phosphotungstic acid under specified conditions.[1-3] Likewise the term "total nitrogen" signifies the entire nitrogen present in an extract sample. The values obtained in either instance are always calculated to the nitrogen content in 1.00 ml. of sample. All determinations of this study were performed in duplicate by a micro-Kjeldahl method based upon Stover and Sandin's[4] procedure (use of boric acid containing methyl red and methylene blue for the titration step) as recommended by Kabat and Mayer.[5]

†Obtainable upon request from The Institute of Allergy, Roosevelt Hospital, New York 19, N. Y.

‡Among these were barley, lima and navy beans, several fish and shellfish, egg white (but not egg yolk), liver, mustard, rice, turkey, veal, and white wheat extracts.

TABLE I. EXAMPLES OF SOME PROTEIN NITROGEN-TOTAL NITROGEN RATIOS AND EXAMPLES OF VARIANCE OF THIS RATIO IN DIFFERENT PREPARATIONS OF THE SAME EXTRACTS

EXTRACTS	PROTEIN NITROGEN (MILLIGRAMS PER MILLILITER)	TOTAL NITROGEN (MILLIGRAMS PER MILLILITER)	PROTEIN NITROGEN (PER CENT OF TOTAL NITROGEN)
Apple 51*	0.051	0.117	43.6
Apple 54	0.041	0.053	77.4
Apricot 53	0.028	0.110	25.5
Banana 51	0.088	0.103	85.4
Bass 51	0.967	1.607	60.2
String bean 50	0.071	0.134	53.0
String bean 53	0.373	1.110	33.6
Beef 50	0.832	1.094	76.1
Beef 51	0.865	0.939	92.1
Broccoli 52	0.085	0.247	34.4
Cantaloupe 50	0.147	0.202	72.8
Cantaloupe 54	0.075	0.132	56.8
Carrot 50	0.132	0.215	61.4
Carrot 52	0.150	0.314	47.8
Chicken 50	0.824	1.317	62.6
Chicken 53	0.582	0.615	94.6
Chocolate 51	0.342	0.524	65.3
Eel 49	0.384	0.589	65.2
Eel 51	0.561	0.565	99.3
Lobster 52	0.339	0.455	74.5
Cow Milk Whey 53	0.952	1.103	86.3
Cow Milk Whey 54	1.167	1.290	90.5
Onion 50	0.389	0.910	42.7
Orange 50	0.199	0.320	62.2
Pork 51	0.450	0.556	80.9
Sardine 49	0.237	0.819	28.9
Strawberry 52	0.035	0.083	42.2
Tomato 50	0.108	0.201	53.7
English Walnut 51	0.116	0.187	62.0
Whole Wheat 52	0.424	0.475	89.3

*The number following the extract indicates the laboratory number of the preparation.

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THE ANTIGENIC RELATIONSHIP OF THE POLLEN, SEED, AND LEAVES OF GIANT RAGWEED

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THE antigenic relationship between ragweed pollen, seed, and leaves is of practical and theoretical interest. It is known that wind-borne particles of plants, other than pollen, can induce coryza, conjunctivitis, and even asthma in susceptible persons. Often patients suffering from ragweed-pollen allergy complain of symptoms on windy autumn days, long after pollen has disappeared from the air. The minute particles of the ragweed leaves and stems, dried by the sun and wind and replacing the pollen, might account for this.

Another practical point of interest with respect to relationship of the antigens of pollen, seed, and leaves is the possible use of the latter two, which are more easily available, as sources of extracts for diagnostic and desensitizing material used in the management of allergic conditions. This study was undertaken not only to elucidate the practical aspect of the problem but also to obtain basic information on the immunologic relationship of the seeds and leaves to pollen.

EXPERIMENTAL PROCEDURES

1. *Materials.*—Giant ragweed pollen was exhaustively defatted with petroleum ether in a Soxhlet apparatus. A 3 per cent weight per volume extract of the pollen in Coca's fluid (1:33) was sterilized by filtration through a Seitz pad and stored at 4° C. All subsequent sterilizations were accomplished in the same manner. Fresh giant ragweed plants were gathered and stored at room temperature until they were completely dry. The seeds were removed, the dried stems and leaves cut into small pieces and ground as finely as possible by passage through a meat grinder. This material was defatted and extracted as described above for pollen. The seeds were similarly ground, defatted, and extracted.

Tests on eight subjects with a history of ragweed pollen hypersensitivity indicate that specific allergens were present in the seeds and stems and leaves.

2. *Fractionation Methods.*—Four fractionation procedures were carried out individually on pollen, seed, and leaves.

a. *Acetone Fractionation:* A 10 per cent extract of pollen in 0.1N NaOH was precipitated by the addition of seven volumes of cold acetone. The supernatant fluid was decanted into an evaporating dish and the acetone allowed

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TABLE I. RESULTS OF INTRADERMAL TESTS WITH ACETONE PRECIPITATE FROM SEED AND LEAVES

SUBJECT NO.	POLLEN EXTRACT CONTROL DILUTION* 1	2	3	4	5	6	SEED EXTRACT CONTROL DILUTION 11	12	13	14	15	16	17	18	SEED ACETONE PRECIPITATE DILUTION 11	12	13	14	15	16	17	18	LEAVES EXTRACT CONTROL DILUTION 11	12	13	14	15	16	17	18	LEAVES ACETONE PRECIPITATE DILUTION 11	12	13	14	15	16	17	18
1	2+	2+	2+	2+	2+	–	2+	2+	2+	2+	2+	–	2+	–	2+	2+	2+	2+	2+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	4+	4+	3+	3+	3+	3+	4+	3+	3+	3+	2+	3+	2+	–	3+	3+	3+	3+	3+	3+	2+	2+	4+	4+	4+	3+	2+	+	3+	+	4+	4+	4+	4+	4+	3+	3+	2+
3	+	±	–	–	–	–	3+	3+	2+	+	–	–	–	–	3+	2+	2+	–	–	–	–	–	3+	2+	2+	+	+	+	–	–	3+	2+	2+	2+	+	+	+	+
4	2+	+	–	–	–	–	2+	2+	+	+	+	+	+	+	2+	2+	2+	2+	2+	+	+	+	2+	+	+	–	–	±	+	+	2+	2+	+	+	+	+	+	+
5	4+	4+	3+	2+	2+	2+	+	+	–	–	–	–	–	–	2+	+	+	–	–	–	–	–	2+	+	–	–	–	–	–	–	+	–	–	–	–	–	–
6	+	±	–	–	–	–	3+	3+	2+	–	–	–	–	–	3+	2+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	±	–	–	–	–	–	–	–
7	2+	±	+	–	–	–	4+	3+	3+	2+	+	±	–	–	4+	3+	3+	2+	2+	±	–	–	2+	±	–	–	–	–	–	–	3+	2+	+	±	–	–	–	–
8	3+	3+	2+	2+	2+	±	4+	3+	3+	2+	±	±	–	–	2+	+	±	–	–	–	–	–	3+	2+	+	±	–	–	–	–	–	–	–	–	–	–	–	–
9	3+	3+	2+	+	±	–	2+	2+	±	–	–	–	–	–	2+	+	+	±	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–

*Dilutions in thousands:

No. 1 = 1:33
No. 2 = 1:90
No. 3 = 1:270
No. 4 = 1:810
No. 5 = 1:2,430
No. 6 = 1:7,290
No. 11 = 1:0.33
No. 12 = 1:1
No. 13 = 1:3
No. 14 = 1:9
No. 15 = 1:27
No. 16 = 1:81
No. 17 = 1:243
No. 18 = 1:729

to evaporate as completely as possible in the air. The residue was dissolved in one-tenth of the original volume of 0.1N NaOH, diluted to 30 per cent with Coca's fluid, sterilized and labeled "pollen supernatant." The precipitate was drained well of acetone and dissolved in one volume of 0.1N NaOH. A portion of this solution, diluted to 3 per cent with Coca's fluid, was sterilized and labeled "pollen acetone precipitate." The remaining portion was allowed to evaporate to dryness in the air, ground finely, dissolved in one volume of 0.1N NaOH, diluted to 3 per cent with Coca's fluid, and sterilized This was labeled "dry acetone precipitate." It is to be noted that "pollen supernatant" was made up ten times as concentrated as the other fractions.

Essentially the same fractionation procedures were carried out on 10 per cent extracts of seeds ("seed extract control") and leaves and stems ("leaves and stem control") except that both "leaves acetone precipitate" and "seed acetone precipitate" were made up as a 10 per cent solution in Coca's.

The above extracts were tested by the scratch procedure in 1:33, 100, 300, 900, 2,700 dilutions on the volar aspects of the arms and forearms or the backs of subjects clinically sensitive to ragweed pollen. The dilutions used for intradermal testing ranged from 1:33,000 to 1:7,290,000 for the pollen extracts and 1:330 to 1:729,000 for the leaves and seeds extracts. The results of the intradermal titrations are shown in Table I. In this and all subsequent titrations control tests done simultaneously on nonallergic subjects gave negative results.

b. *Dioxane and ammonium sulfate fractionations:* This technique was essentially the same as described by Boatner and Efron[1] except that dioxane was added to the extracts gradually, with continuous shaking. Fractions isolated by this procedure were a "25 per cent dioxane fraction," a "75 per cent dioxane fraction" and an "ammonium sulfate fraction."

The "pollen extract control" was tested simultaneously with the above fractions using the same dilutions for the intradermal tests as in the previous experiments. For the scratch tests, the dilutions were 1:10, 30, 100, 300, 1,000, 3,000, and 10,000. The sites chosen were the same as before. The results of the scratch test are presented in Table II.

TABLE II. RESULTS OF SCRATCH TESTS WITH CONTROL EXTRACTS OF POLLEN, SEED AND LEAVES

SUBJECT NO.	SCRATCH TEST WITH 1:33 EXTRACT		
	POLLEN	SEED	LEAVES
1	2+	-	-
2	4+	2+	2+
3	4+	2+	2+
4	±	±	-
5	+	-	+
6	±	-	-
7	±	-	-
8	2+	-	-
9	-	-	-

c. *Acetone and dioxane fractionation:* To the cold solution of "pollen acetone precipitate" sufficient cold dioxane was slowly added to make a 25 per cent concentration. The precipitate was collected by centrifugation and made up

TABLE IIA

Results of Scratch Tests With Dioxane and Ammonium Sulfate Precipitate From Pollen Extract

SUBJECT NO.	POLLEN EXTRACT CONTROL DILUTION*						POLLEN 25% DIOXANE FRACTION DILUTION						POLLEN 75% DIOXANE FRACTION DILUTION						POLLEN AMMONIUM SULFATE FRACTION DILUTION					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	3+	+	±	−	−	−	+	+	±	−	−	−	+	±	−	−	−	−	−	−	−	−	−	−
2	3+	3+	+	+	±	−	+	±	−	−	−	−	−	−	−	−	−	−	+	±	−	−	−	−
3	4+	3+	2+	−	−	−	2+	+	±	−	−	−	2+	±	±	−	−	−	2+	2+	±	±	±	±
4	4+	4+	4+	3+	2+	+	2+	2+	+	−	−	−	3+	+	2+	±	−	−	3+	3+	3+	+	±	−
5	4+	2+	+	+	+	+	+	+	−	−	−	−	2+	±	±	±	±	±	2+	2+	+	−	−	−

Results of Scratch Tests With Dioxane and Ammonium Sulfate Precipitate From Seed and Leaves Extract

SUBJECT NO.	POLLEN EXTRACT CONTROL DILUTION*						POLLEN 75% DIOXANE FRACTION DILUTION						POLLEN AMMONIUM SULFATE FRACTION DILUTION						SEED EXTRACT CONTROL DILUTION						SEED 75% DIOXANE FRACTION DILUTION						LEAVES EXTRACT CONTROL DILUTION						LEAVES 75% DIOXANE FRACTION DILUTION					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	4+	4+	4+	2+	+	−	+	+	−	−	−	−	4+	3+	2+	2+	±	−	2+	2+	±	−	−	−	+	±	−	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−
2	2+	+	−	−	−	−	−	−	−	−	−	−	2+	±	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−
3	2+	+	±	±	−	−	2+	2+	±	−	−	−	4+	2+	+	−	−	−	±	±	−	−	−	−	−	−	−	−	−	−	±	±	−	−	−	−	−	−	−	−	−	−

*Dilution No. 1 = 1:10, 2 = 1:30, 3 = 1:100, 4 = 1:300, 5 = 1:1,000, 6 = 1:3,000.

to the original volume with 0.1N NaOH and sterilized. This was labeled "acetone-25 per cent dioxane fraction." Additional dioxane was added to the supernatant to make a 75 per cent concentration. The precipitate was redissolved in one volume 0.1N NaOH and divided into two portions. One portion was sterilized and will be referred to as "acetone-75 per cent dioxane fraction." The second portion was fractionated by ammonium sulfate as described in section 2b; the preparation will be referred to as "acetone-dioxane-ammonium sulfate fraction." Tests were made by the scratch method.

d. *Sodium Benzoate and Acetone Fractionation:* This method was carried out essentially according to McIntire's modification[6] of that of Rimington and associates.[7] To one volume of 10 per cent extract control was added sodium benzoate, 4 Gm. per 100 ml. Concentrated hydrochloric acid was added dropwise with continuous stirring of the solution until a pH of at least 3.5 was reached. After chilling for 10 to 15 hours in the refrigerator, the precipitated benzoic acid was collected by suction filtration on a Büchner funnel, without washing, and the suction was continued until the filter cake was nearly dry. The filter cake was treated with 9 times its weight of acetone. The suspension was centrifuged, the supernatant discarded, and the precipitate dissolved in one-half volume of Coca's extracting fluid. This "sodium benzoate fraction" was made up in the same dilutions as in the previous experiment and tested by the scratch technique.

3. *Comparative Clinical Studies.*—In order to evaluate these fractions with respect to their reactivity titrations were carried out simultaneously on the same subject in three ragweed-sensitive patients. Table III indicates the representative results obtained by intradermal testing in one of these subjects (K. S.).

RESULTS

1. *Purified Extracts.*—a. In skin reactivity "pollen acetone precipitate" was about one-third as strong as the "pollen extract control." When compared by cutaneous response in different subjects "dry acetone precipitate" ranged from one-tenth to one-third of the strength of the "pollen acetone precipitate" and one-thirtieth to one-ninth of the strength of the "pollen extract control." The "pollen supernatant," although used for skin testing in tenfold concentration, gave only mild reactions in two patients.

The control extracts and the acetone precipitated preparations of seed and leaves were tested simultaneously with "pollen extract control" but in a tenfold stronger concentration.

b. During the process of purification by dioxane precipitation there was a successive loss of pigment. Much of the plant pigment was lost also by absorption on the Seitz pad during filtration. The greater portion of dioxane insoluble material precipitated out at 25 per cent concentration. The precipitates were gummy and difficult to redissolve. The antigenic potency of the 25 per cent and 75 per cent dioxane fractions as measured by cutaneous response was weaker than that of each of the control extracts. The ammonium sulfate fractions generally gave a stronger response than did either of the two

dioxane fractions. The ammonium sulfate fraction of leaves, however, gave a weaker reaction than did the 75 per cent dioxane fraction and the control leaf extract.

c. The cutaneous response to the acetone-25 per cent dioxane fraction of pollen was about one-tenth as strong as the acetone-75 per cent dioxane fraction. The acetone-dioxane-ammonium sulfate fraction was from 3 to 100 times as potent as the acetone-75 per cent dioxane fraction but only about one-tenth to one-third the potency of the 10 per cent pollen control extract, even though it was made up twice as concentrated as the original.

d. The sodium benzoate fraction of pollen in a 20 per cent concentration gave about the same average result as did a 10 per cent concentration of the ammonium sulfate fraction.

TABLE III. RESULTS OF INTRADERMAL TESTS WITH FRACTIONS OF POLLEN, SEED, AND LEAVES

SUBJECT	PREPARATION	DILUTIONS* 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
K. S.	Pollen extract control						4+	3+	2+	2+	2+	2+	2+	2+	+	-
	Pollen acetone precipitate			4+	3+	3+	2+	+	+	+	+	-				
	Pollen ammonium sulfate fraction			4+	3+	3+	2+	2+	2+	2+	2+	+	±			
	Pollen sodium benzoate fraction				3+	2+	+	+	±	-						
	Seed extract control	2+	2+	+	+	-										
	Seed acetone precipitate	4+	3+	2+	±											
	Seed ammonium sulfate fraction	4+	3+	2+	±	-										
	Seed sodium benzoate fraction	4+	3+	+	±	-										
	Leaves extract control	4+	4+	3+	3+	2+	+	±	-							
	Leaves acetone precipitate	3+	3+	2+	2+	±	-	-								
	Leaves ammonium sulfate fraction	+	-	-												
	Leaves sodium benzoate fraction	2+	+	-												

*Dilution No. 1 = 1:10
2 = 1:100
3 = 1:1,000
4 = 1:10,000
5 = 1:30,000
6 = 1:90,000
7 = 1:270,000
8 = 1:810,000
9 = 1:2,430,000
10 = 1:7,290,000
11 = 1:21,870,000
12 = 1:65,610,000
13 = 1:196,830,000
14 = 1:590,490,000
15 = 1:1,771,470,000

2. *Skin Tests in Allergic Subjects.*—The results of simultaneous and comparative titrations done with all preparations indicate that fractionation with acetone produces a preparation which is somewhat less potent than the control extract. Subsequent fractionations with ammonium sulfate and benzoic acid result in progressively less potent preparations. This pattern of reactivity is reflected for pollen, leaves, and seeds in that order, indicating that the same reagin-reacting antigen is separated from each substrate in approximately the same ratio by parallel fractionation. Although there is a certain amount of variation for each individual subject, an over-all pattern does seem to exist.

3. *Passive Transfer and Reagin Exhaustion Tests.*—Passive transfer sites with human ragweed reagin were prepared on the backs of nonallergic human subjects. After 48 hours the control extracts of pollen, seeds, and leaves were

titrated by the intradermal technique. That dilution of each extract which gave a 2+ reaction was used to exhaust a row of passively sensitized sites by repeated daily or twice daily injections of 0.2 ml. of extract until no further local reaction (erythema or wheal formation) occurred. Cross reactivity to each of the other two antigens was determined the day following complete exhaustion. The results which are given in Table IV indicate that pollen antigen completely exhausted the test sites so that no cutaneous response was elicited by either leaf or seed antigen.

The sites exhausted by seed antigen always gave positive and significant reactions on challenge with the pollen extract. Similar sites challenged with the leaf antigen resulted in positive reactions in three subjects, a doubtful reaction in one, and negative reaction in two.

Sites exhausted by the leaf extract gave inconsistent results when challenged with the pollen extract. Two subjects showed a strong response, one, a suggestive, and three, none. When challenged with seed antigen there was no reaction at the sites.

4. *Anaphylaxis in the Guinea Pig.*—Each of the 44 guinea pigs weighing 300 to 500 grams was sensitized by injecting 3 ml. of a mixture of 10 per cent giant ragweed pollen extract in Freund's adjuvant. Eighteen days after sensitization the animals were challenged by intravenous administration of one of the fractionated preparations. The volume of the challenge dose was adjusted so that each animal received 0.2 mg. total nitrogen. After fifteen days the same animals were challenged with 0.2 mg. protein N. The results are submitted in Table V.

The strongest anaphylactic reactions were shown by the guinea pigs challenged with pollen extract control based on either total or protein nitrogen. On the basis of the total nitrogen content the next potent preparation was the ammonium sulfate fraction of pollen. When tested on the protein nitrogen basis the sodium benzoate and the ammonium sulfate fractions of pollen were next and were of comparable potency.

5. *Precipitin Test.*—Two-tenths milliliter of rabbit antiragweed pollen serum diluted 1:3 was placed in each of several precipitin tubes. A similar volume of antigen solution containing 0.024 mg. total nitrogen and in multiple dilutions of 1:5 was layered over the serum and the tubes incubated for 1 hour at 37° C. After the interfacial zone was examined for a precipitin ring, the contents of the tubes were well mixed and stored at 4° C. for 24 hours. The degree of precipitation indicating a reaction was then recorded. A similar comparative titration was carried out with the various preparations based on a protein nitrogen content of 0.007 mg. A similar precipitin test was carried out using that concentration of antigen which gave a 2+ cutaneous response in subject K. S.

The highest titers were obtained with pollen extract control and ammonium sulfate fractions of pollen and leaves on the basis of either the total nitrogen or protein nitrogen content.

DISCUSSION

As a result of the many investigations on its antigenicity and chemistry, the tissue of the giant ragweed which has been best characterized is the pollen. Present knowledge concerning the antigens of ragweed pollen is far from complete, however, and most investigators agree that the antigenic makeup of the extract is quite complex. For these reasons, the results of experiments with all dilutions of the extracts of the leaves and seeds were compared with those obtained with the same dilutions of pollen control extracts as the standard.

The results obtained with skin testing emphasize the individual differences in sensitivity that subjects will exhibit to a given extract. In spite of a different threshold of reactivity to the same dilutions of pollen fractions, however, there was, in general, a similar pattern of responsiveness to the antigens of the three tissues of the giant ragweed. The reagin exhaustion studies suggest that in addition to unrelated antigens there exists a common antigen.

The possibility that some denaturation may have occurred during the fractionation procedures with modification in antigenic behavior is not to be overlooked. Thus, the response in the allergic subject to the fractions of the same tissue was not in proportion to the total nitrogen or to the protein nitrogen content per unit of volume. Also, the ability of each of the extracts of the three plant tissues to sensitize guinea pigs was not proportional to the protein or total nitrogen content. Of the fractionation procedures studied, the ammonium sulfate fractionation of pollen and leaf extract seemed to produce the most potent preparations, even though they contained the least amount of total nitrogen. Paradoxically, ammonium sulfate fractionation of the acetone-precipitable material did not result in a more potent fraction.

The cross reactivity which demonstrates the antigenic relationship between the fractions is best evident from the results of anaphylaxis in the guinea pig (Table V) and the precipitin test. Thus, we disagree with the findings of Thommen,[8] who did not obtain cross reactivity between tissues of the same plant using extracts made from the leaf, stem, roots, and seed of giant ragweed and of timothy. The results of Duke[2] also refute the concept of the antigenic relationship of different parts of the plants. Wartenberg[12] observed a difference in the serologic behavior of different parts of plants. Dunbar[3] noted that extracts of the pollen, grain, and leaf of rye showed a high degree of specific reactivity based on the results of the complement fixation test. Wodehouse[13] was able to differentiate between pollen and seeds by their anaphylactic properties.

The results of Vallery-Radot and associates,[9] however, based on their studies on the pollen, stem, and roots of the plant, *Dactylis glomerata* (orchard grass), support the likelihood of antigenic relationship of the different tissues of the plant. Comparable skin reactions were observed by testing with the pollen and stem extracts. The extract of the root failed to show any reaction. Waring and Pope[11] have reported that patients who are sensitive to the pollen of the cottonwood trees are also sensitive to the hair tufts of the seed.

TABLE IV. PASSIVE TRANSFER AND REAGIN EXHAUSTION

SUBJECT NO.	SITES EXHAUSTED WITH POLLEN EXTRACT CONTROL		SITES EXHAUSTED WITH SEED EXTRACT CONTROL		SITES EXHAUSTED WITH LEAVES EXTRACT CONTROL	
	CROSS TESTED WITH EXTRACT CONTROL OF		CROSS TESTED WITH EXTRACT CONTROL OF		CROSS TESTED WITH EXTRACT CONTROL OF	
	SEED	LEAVES	POLLEN	LEAVES	POLLEN	SEED
1	–	–	2+	–	–	–
2	–	–	±	2+	–	–
3	–	–	2+	2+	–	–
4	–	–	3+	3+	±	–
5	–	–	3+	–	2+	–
6	–	–	3+	–	3+	–

Dutton,[4] found that beet pollen and beet seed dust caused hay fever and asthma in patients sensitive to beets. Grubb and Vaughan,[5, 10] studying group and species specific allergens of pollen and foods by clinical, chemical, and immunologic procedures, came to the conclusion that about one-half of those patients allergic to the pollen of wheat, corn, and beet were also allergic to the corresponding food.

TABLE V. ANAPHYLACTIC SHOCK IN GUINEA PIGS SENSITIZED WITH POLLEN EXTRACT CONTROL AND CHALLEGED WITH POLLEN, SEED, AND LEAF FRACTIONS

TISSUE OF THE PLANT	GUINEA PIG NO.	EXTRACT CONTROL	GUINEA PIG NO.	ACETONE PRECIPITATE FRACTION	GUINEA PIG NO.	AMMONIUM SULFATE FRACTION	GUINEA PIG NO.	SODIUM BENZOATE AND ACETONE FRACTION
Total Nitrogen Basis (0.2 mg. Total N./Dose)								
Pollen	1	4+	10	–	19	2+	28	±
	2	3+	11	–	20	4+	29	+
	3	+	12	±	21	4+	30	–
Seed	4	–	13	–	22	–	31	–
	5	–	14	–	23	–	32	–
	6	–	15	–	24	–	33	–
Leaves	7	–	16	–	25	–	34	–
	8	±	17	–	26	±	35	–
	9	–	18	+	27	±	36	–
Protein Nitrogen Basis (0.2 mg. Protein N./Dose)								
Pollen	1	4+	10	±	19	+	27	3+
	2	4+	11	–	20	2+	28	2+
	3	3+	12	–	21	3+	29	±
Seed	4	–	13	2+	22	–	30	–
	5	–	14	+	23	–	31	–
	6	–	15	±	24	–	32	±
Leaves	7	±	16	–	25	4+	33	–
	8	–	17	–	26	4+	34	–
	9	–	18	±			35	±

SUMMARY

Fractions of the giant ragweed pollen, seed, and leaves were prepared in a purified form. The antigenic relationships of these preparations were compared by direct skin tests in ragweed-sensitive patients, by cross testing of reagin sites exhausted with a related antigen, by anaphylaxis and by precipitin tests. The results showed that:

1. There exists an antigenic relationship of the three investigated giant ragweed tissues.

2. Comparative titrations suggest a difference in potency decreasing from pollen through leaves to seed.

3. There seems to be a very close relationship between the leaf and pollen antigen. The seed does not contain an antigen present in the pollen in that it is not capable of exhausting sites inoculated with human reagin. The restricted number of tested subjects, however, does not allow final conclusions to be drawn on this point.

4. Quantitative titrations and other investigations showed that ammonium sulfate fractionation results in the most potent preparations for leaves and pollen, but acetone fractionation is apparently required to produce potent seed preparations, especially as observed by its anaphylactic properties in sensitized guinea pigs.

5. The relatively small amount of pollen antigen in the leaves and seed would speak against the use of these plant tissues as a practical source of the antigen for diagnostic and therapeutic purposes.

6. The results suggest that the plant debris may serve as a natural source of allergy to the pollen-sensitive patient. Further work would have to be done before this can be accepted as a final opinion.

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TOPICAL USE OF HYDROCORTISONE AND HYDROCORTISONE-NEOMYCIN OINTMENTS IN ALLERGIC DERMATOSES

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THE present study summarizes observations made during the past year on the use of topically applied hydrocortisone, or compound F, in a fairly large group of patients with representative allergic skin eruptions. There is considerable experimental as well as clinical evidence indicating that hydrocortisone differs from cortisone, at least quantitatively, in its local effect on tissues.[1] While it is well known that cortisone is capable of influencing the course of many types of allergic dermatoses when administered by oral or parenteral routes, very little, if any, response is evident when it is applied directly to cutaneous lesions,[2, 4] although it is highly effective on local application in certain diseases of the eye.[5] Hydrocortisone appears even more effective than cortisone in the local treatment of similar ocular conditions[6]; in its direct action on inflamed joints[7]; and in its local effect on certain inflammatory cutaneous lesions.[8, 9] Its value in the clinical management of atopic dermatitis and certain other eczematous eruptions has also been reported.[3, 4] Our own clinical trials of suitable preparations of hydrocortisone in ointment form indicated a marked influence on eczematous and some papulosquamous lesions, and little or no effect on urticarial type of eruptions. The cases included in the present summary are those of atopic and contact dermatitis, as well as certain other possible allergic eruptions, and a small number of nonallergic dermatoses.

It must of course be emphasized that any favorable effect which may ensue from the use of locally applied hormones in allergic dermatoses is entirely symptomatic in nature, and does not influence the underlying etiologic mechanism involved. Such relief, however, though temporary in nature, is a valuable adjunct in the management of these conditions, at least until a more adequate solution of the problem can be attained through the control or correction of basic underlying mechanisms. In addition, the advantages of successful local steroid therapy are considerable when the attendant side effects of systemic hormonal treatment are considered.

MATERIALS AND METHODS

The following preparations were used in this study:*

1. Ointment hydrocortisone (alcohol), 25 mg. per gram.

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*The materials used in this study were supplied by H. F. Hailman, M.D., Ph.D., Medical Division, Dept. of Clinical Investigation, The Upjohn Company, Kalamazoo, Mich. The concentrations of hydrocortisone acetate in wool fat base are available under the trade name, Cortef; the hydrocortisone acetate neomycin sulfate in wax-cholesterol base is available under the trade name, Neo-Cortef.

2. Ointment hydrocortisone acetate, 25 mg. per gram.
3. Ointment hydrocortisone acetate, 10 mg. per gram.
4. Placebo base corresponding to the previously mentioned preparations and consisting of the following:

   25 per cent white mineral oil
   20 per cent wool fat, U.S.P.
   54 or 52.5 per cent white petrolatum
5. Ointment hydrocortisone acetate, 10 mg. and neomycin sulfate, 5 mg. per gram.
6. Ointment hydrocortisone acetate, 25 mg. and neomycin sulfate, 5 mg. per gram.
7. Ointment neomycin sulfate, 5 mg. per gram.

The latter three ointments were supplied in a multi-wax cholesterol base of the following composition:

4 per cent multi-wax
0.5 per cent cholesterol, U.S.P.
0.02 per cent methylparaben, U.S.P.
0.18 per cent n-Butyl-p-hydroxybenzoate
20 per cent white mineral oil q.s. ad white petrolatum.

The majority of the patients utilized in this study were under our direct care for some period of time prior to the use of hydrocortisone ointments, and were seen at least once, and often twice, weekly during the observation period. Many had received, or were receiving, oral or parenteral steroid hormone therapy to relieve their symptoms. The majority had been studied, or were under study, from an allergic point of view, and some were receiving allergic management in addition to symptomatic measures.

As far as possible, the hydrocortisone ointments supplied to the patients were used initially two or three times daily in an involved area of the skin for one week and a placebo ointment base in a corresponding area, in a manner similar to that described by Sulzberger and co-workers.[3, 4] To further confirm the results in cases of chronic dermatitis, the ointment was withdrawn after an initial treatment period for a sufficient time to assess the effects without the ointment. Subsequently, it was again used for an additional period depending upon its effects. In many instances hydrocortisone ointment and placebo base were alternated over a period of months without the patient's knowledge in order to more objectively ascertain the relationship of the ointment to any improvement. Similar procedures were employed in comparing the effectiveness of hydrocortisone (alcohol) and hydrocortisone acetate; in comparing different concentrations and different ointment bases; and in the estimation of the effectiveness of neomycin combined with hydrocortisone.

Early in the study, 2½ per cent ointments were used initially in all cases, with subsequent trial of the lesser strength for maintenance therapy. Later, a number of patients received the 1 per cent ointment initially, and, if the response was not entirely favorable, an effort was made to substitute the higher concentration. Still later in the study, some patients were started on

hydrocortisone-neomycin combinations, while others previously receiving hydrocortisone were transferred to the antibiotic-containing preparation.

In evaluating the results, improvement of 75 per cent or greater was considered as marked; 50 to 75 per cent as moderate; 25 to 50 per cent as slight; and less than 25 per cent as no improvement.

RESULTS

When improvement occurred from the use of hydrocortisone ointment, it was usually rapid and very striking, often evident within the first twenty-four to forty-eight hours, progressing to a maximum response by the end of the first week of treatment. In chronic states, where underlying exciting factors were uncontrolled, recurrence of the dermatitis was generally noted within two or three days following cessation of therapy, although in some instances the remission was more prolonged. Usually it was found necessary to continue application of the ointment once or twice daily to maintain improvement in treated areas. Some patients with chronic dermatitis have been maintained successfully for as long as ten months, at the time of this writing, while others have relapsed despite initial improvement for a considerable period of time.

The most satisfactory response occurred in excoriated, papulovesicular, scaling, and lichenified lesions. Urticarial and deep vesicular lesions responded least favorably. While the use of ointment preparations in acute stages, with oozing or weeping and crusted lesions is generally avoided, a favorable response was frequently observed in such stages following applications of hydrocortisone ointments. In secondarily impetiginized eruptions, a combination of neomycin and hydrocortisone frequently proved efficacious. This will be discussed in a subsequent section.

Comparison of Hydrocortisone (Alcohol) and Hydrocortisone Acetate Ointments.—It was decided early in this study to compare the local effect of free hydrocortisone (alcohol) and hydrocortisone acetate, because of a difference in response reported when these two forms were injected into cutaneous lesions. Goldman and his associates[10] have indicated that compound F acetate injected locally exerts a definite inhibitory inflammatory effect on a variety of dermatologic lesions, while the free alcohol of compound F is not similarly active. From the work of Conn, Louis, and Fajans[11] it appears that a greater metabolic response follows the intramuscular injections of the free alcohol, while oral preparations of both the acetate and free compound F induce approximately the same effects. This difference has been attributed to a slower rate of absorption of the acetate ester from the intramuscular depot.[12]

Fifteen patients in various age groups with atopic dermatitis were treated with 2½ per cent hydrocortisone (alcohol), and hydrocortisone acetate incorporated in the same base, as well as with the ointment base itself. No essential difference in effect was discernible between the two forms of hydrocortisone. Both appeared equally effective or ineffective in the same patient. Since no difference in the action of these forms was observed on local application, supplies of hydrocortisone acetate in ointment form were made available, and used in the balance of the study.

Atopic Dermatitis.—Seventy-three patients utilized in this study were classified under this diagnostic heading. The group consisted of 29 infants and children, from 8 months to 14 years of age, and 44 adults ranging in age from 14 to 78 years. The duration of the disease was at least three months, and for as long as forty years.

From Table I it will be seen that 20 of 37 adults initially given the 2½ per cent ointment showed marked improvement; 11 were benefited less, while no help occurred in 3. Aggravation of the dermatitis was recorded in 3 others. In 7 adults initially given the 1 per cent ointment, 1 was markedly benefited; 4 achieved a slight to moderate response; while 2 were not helped.

In 15 infants and children initially given 2½ per cent hydrocortisone, 9 were markedly improved; benefit was slight to moderate in 4; and no improvement occurred in 2. Where the 1 per cent strength was used initially in 14 youngsters, marked improvement occurred in 11; 2 showed a slight to moderate response; and 1 was not benefited.

TABLE I. HYDROCORTISONE ACETATE OINTMENTS. RESULTS IN ATOPIC DERMATITIS

AGE GROUP	STRENGTH OF OINTMENT	TOTAL NO. OF PATIENTS TREATED	NUMBER SHOWING IMPROVEMENT			
			MARKED	SLIGHT TO MODERATE	NONE	AGGRAVATED
Adults	2½%	37	20 (54%)	11 (30%)	3 (8%)	3 (8%)
	1 %	7	1 (14%)	4 (57%)	2 (28%)	0
Infants and children	2½%	15	9 (60%)	4 (26%)	2 (13%)	0
	1 %	14	11 (78%)	2 (14%)	1 (7%)	0
Total		73	41 (56%)	21 (28%)	8 (11%)	3 (4%)

Since it appeared that many patients, especially infants and children, obtained an excellent response from the 1 per cent concentration, comparisons between the two strengths were made in a number of cases. As will be seen from Table II, approximately one-third of those markedly benefited by the 2½ per cent ointment were similarly helped by a 1 per cent concentration. The remainder noted a less favorable response. Where the initial effect of 2½ per cent ointment was less than maximal, the result with the 1 per cent concentration was generally poor. In patients whose initial response to 1 per cent hydrocortisone was moderate, slight, or negligible, a stronger ointment was often more effective.

TABLE II. HYDROCORTISONE ACETATE OINTMENTS. COMPARISON OF 2½ PER CENT AND 1 PER CENT OINTMENT CONCENTRATION IN SAME PATIENTS

WHERE INITIAL RESPONSE TO 2½ PER CENT OINTMENT WAS	TOTAL NO. OF CASES	RESPONSE TO 1 PER CENT OINTMENT WAS		
		MARKED	SLIGHT TO MODERATE	NONE
Marked	20	7	9	4
Slight to moderate	7	0	1	6

WHERE INITIAL RESPONSE TO 1 PER CENT OINTMENT WAS	TOTAL NO. OF CASES	RESPONSE TO 2½ PER CENT OINTMENT WAS		
		MARKED	SLIGHT TO MODERATE	NONE
Slight to moderate	6	4	2	0
None	3	0	2	1

We would assume from these observations that the lesions of atopic dermatitis usually encountered in infants and children are more readily influenced by local hydrocortisone, and that the 1 per cent ointment is frequently sufficient. In older individuals with more chronic, long-standing, and extensive involvement, initial use of a concentrated ointment is more likely to prove effective, although maintenance of improvement with the lesser strength may be possible.

Contact Dermatitis.—In 30 patients with eczematous contact-type dermatitis (Table III), the effects of 2½ and 1 per cent hydrocortisone ointments were considered excellent in 16; slight to moderate in 10; and negligible in 3. One patient was made worse by application of the ointment.

The results with this material in erutions involving the eyelids, face, or axillae due to cosmetic agents were exceedingly good. The offending contact allergen in each instance was suspected at the time treatment was instituted and was later confirmed by patch test. Further contact was avoided and subsequent recurrence of the dermatitis was not observed after the ointment was discontinued.

TABLE III. HYDROCORTISONE ACETATE OINTMENTS. RESULTS IN CONTACT DERMATITIS

ETIOLOGICAL FACTOR	NO. OF CASES	NUMBER SHOWING IMPROVEMENT			
		MARKED	SLIGHT TO MODERATE	NONE	AGGRAVATED
Cosmetics	7	5	2	0	0
Plant oils	6	1	3	1	1
Clothing and dyestuffs	5	3	2	0	0
Local medicaments	3	1	2	0	0
Occupational	3	3	0	0	0
Undetermined	6	3	1	2	0
Total	30	16	10	3	1

In acute dermatitis due to plant oils, the results with local hydrocortisone alone were not as striking. It was frequently necessary to supplement this therapy with other local and general measures to arrest the course of the dermatitis. One patient in this group appeared aggravated by the ointment and was hospitalized for ACTH therapy.

Dermatitis due to fabrics, dyestuffs, local medicaments, and occupationally encountered chemicals responded for the most part quite favorably to local hydrocortisone therapy and proved exceedingly valuable until the exciting factor could be determined, and measures to avoid or eliminate it instituted. Where the contactant could not be readily identified, hydrocortisone often proved helpful in controlling the dermatitis over a period of months, despite the probability that the patient was presumably still in contact with the offending substance.

Dermatitis of the Hands.—The effect of hydrocortisone ointments in 29 cases of dermatitis limited to the hands (Table IV) is considered separately because of the frequently wide divergence in interpretation of etiologic mechanisms involved. Not included in this group are those cases in which involvement of the hands was accompanied by lesions elsewhere on the skin.

Under chronic eczema of the hands, we have considered 22 patients with chronic, recurrent, eczematous eruptions involving both the dorsal and volar aspects of the fingers and hands, who were originally referred for allergic study. The duration of dermatitis was at least six months and for as long as eight years. Eighteen were women, aged 15 to 57 years; while only 4 were men, aged 22 to 50 years. All had received rather extensive local dermatologic therapy prior to the use of this medication.

TABLE IV. HYDROCORTISONE OINTMENTS. RESULTS IN DERMATITIS LIMITED TO THE HANDS

CLASSIFICATION	TOTAL CASES	IMPROVEMENT			
		MARKED	SLIGHT TO MODERATE	NONE	AGGRAVATED
Chronic eczema	22	6	8	5	3
Contact eczema	5	2	2	1	0
Pompholyx	1	0	0	0	1
Psoriasis	1	0	0	1	0
Total	29	8	10	7	4

As will be seen in Table IV, the effects of hydrocortisone ointment were very favorable in 6 cases, and somewhat less so in 8 others. Five patients were not helped, and 3 became worse following its use.

In contact dermatitis limited to the hands, some degree of improvement was recorded in 4 out of 5 cases.

A patient with palmar psoriatic lesions was not benefited, while one with an acute deep vesicular eruption limited to the palms of both hands appeared worse after its use.

Miscellaneous Dermatoses.—During the course of these observations, a number of possibly allergic and nonallergic dermatoses were treated with hydrocortisone ointments (Table V). One of 6 cases of psoriasis achieved slight benefit, while the remainder were not favorably influenced by daily applications, over periods of two to four weeks.

TABLE V. HYDROCORTISONE ACETATE OINTMENTS (2½ PER CENT). RESULTS IN MISCELLANEOUS DERMATOSES

DIAGNOSIS	NO. OF CASES	NUMBER SHOWING IMPROVEMENT			
		MARKED	SLIGHT TO MODERATE	NONE	AGGRAVATED
Psoriasis	6	0	1	5	0
Pruritus ani	5	1	0	3	1
Seborrheic dermatitis	5	1	3	1	0
Lichen simplex chronicus	4	4	0	0	0
Otitis externa	4	3	1	0	0
Infectious eczematoid dermatitis	2	2	0	0	0
Lupus erythematosus—discoid type	1	0	0	1	0
Total	27	11	5	10	1

In 5 patients with pruritus ani, one who also had atopic dermatitis and bronchial asthma was markedly relieved following its use. Two who originally developed their difficulty in associations with Aureomycin therapy were not benefited. In the remaining 2 patients, both long-standing intractable cases, one was not helped, while the other complained that the symptoms were

made worse by the ointment. This latter patient was subsequently hospitalized and failed to respond favorably either to ACTH therapy or to a surgical procedure consisting of undercutting the anal and perianal skin. It should be pointed out that a much better response with hydrocortisone ointment has recently been reported by others in a larger series of severe intractable pruritus ani.[4, 13]

In 5 cases of seborrheic dermatitis of the scalp, forehead, and face, one patient was very substantially benefited; 3 were slightly or moderately improved; while one was not helped.

A very favorable response occurred in each of 4 patients with localized, chronic, lichenified lesions on the neck or extremities.

Relief of itching and scaling was evident in 4 patients with chronic eczema of the external auditory canal. In 2 of these cases, the results with the hydrocortisone-neomycin combination appeared better than with hydrocortisone alone, and very much better than with neomycin ointment alone. A similar result was noted in 2 cases of infectious eczematoid dermatitis, one resulting from a chronic draining ear, and the other associated with an irritating nasal discharge.

One patient with discoid erythematosus was not benefited by daily treatment of the lesions over a period of one month.

Hydrocortisone-Neomycin Combinations.—The combination of an effective antibiotic with hydrocortisone is a logical development in the local therapy of certain dermatoses, since there are frequent instances where eruptions susceptible to the favorable influence of topical hydrocortisone are complicated by secondary infection. It must also be recalled that during systemic administration of steroid hormones, a suppressive effect of inflammation occurs with a reduction in phagocytic activity, facilitating the spread of microorganisms.[1, 14] That this may also become more evident with extensive local use of hydrocortisone must be deemed possible.

The choice of neomycin as the antibiotic used in conjunction with hydrocortisone in the present study is based on its high effectiveness in controlling a wide range of microorganisms encountered in skin infections. Excellent control of cutaneous infection has been reported with the topical application of ointments containing similar concentrations of neomycin (5 mg. per gram).[15, 16] In addition, the incidence of cutaneous sensitization following the local use of this antibiotic has been extremely low. The possibility of localized moniliasis after its prolonged use has been pointed out.[15] In the preparation used in this study, two agents, methylparaben and n-Butyl-p-hydroxybenzoate, possessing antifungal activity of a low order, were included in the wax-cholesterol ointment base. Data concerning their effectiveness in suppressing fungal growth on the skin are not available.[17]

During the course of this study, 30 patients were encountered who presented dermatoses complicated by secondary infection. Two of these were actively using hydrocortisone ointment when infection supervened. It was possible to compare the effectiveness of hydrocortisone and hydrocortisone-neomycin ointment in 20 of these patients. Four were not benefited by either

preparation, 2 were equally improved, and 14 achieved a more rapid improvement of both the infection and underlying dermatosis in the areas treated with the antibiotic-containing ointment.

Sixty-five patients with eruptions uncomplicated by infection who were using, or had previously used, hydrocortisone ointment with some degree of success were transferred to the neomycin-containing preparation without their knowledge. The improvement in 2 patients, both cases of otitis externa, appeared somewhat greater with hydrocortisone-neomycin ointment, while the response in the remaining 63 cases was approximately the same.

Sensitivity and Resistance.—In the entire group of 159 patients reported in this study, the dermatitis in 9, or 5.6 per cent, became worse following the

TABLE VI. AGGRAVATION OF DERMATITIS FOLLOWING HYDROCORTISONE OINTMENTS

CASE NO.	DIAGNOSIS	AGE	OINTMENT STRENGTH AND BASE	CAUSE
1	Atopic dermatitis	17	2½%—Wool-fat	Lanolin
2	Atopic dermatitis	37	2½%—Wool-fat	Lanolin, petrolatum
3	Atopic dermatitis	22	2½%—Wool-fat	Lanolin
4	Chronic eczema of hands	24	2½%—Wool-fat 2½%—Wax-cholesterol	Petrolatum
5	Chronic eczema of hands	27	2½%—Wool-fat	Petrolatum
6	Chronic eczema of hands (acute stage)	35	1%—Wool-fat	Primary irritation
7	Poison ivy dermatitis	37	2½%—Wool-fat 2½%—Wax-cholesterol	Primary irritation
8	Pompholyx	42	2½%—Wax-cholesterol	Primary irritation
9	Pruritus ani	41	2½%—Wool-fat	Undetermined

local use of one of the ointment preparations (Table VI). Specific sensitization to hydrocortisone or neomycin could not be demonstrated in any of these cases. At least 6 patients were felt to be sensitive to the ointment base used to incorporate the active materials, as determined by patch test or repeated application of the base to areas of dermatitis and uninvolved skin. Two patients appeared to be irritated due to the use of an ointment during an acute phase of their dermatitis, where bland local therapy would perhaps have been indicated. In one patient the cause of aggravation was not determined.

Among those who became worse after treatment were 3 adults with atopic dermatitis determined to be sensitive to the wool-fat base. It is interesting that one of these was found intolerant to the placebo base at the onset of treatment, but was able to attain moderate improvement from hydrocortisone incorporated in the same vehicle for several months before aggravation from this preparation was also noted. It is presumed that for a period of time her sensitivity to the base was counteracted by the anti-inflammatory effects of hydrocortisone.

Two of three patients with chronic eczema of the hands who were made worse during the course of treatment with hydrocortisone ointments were felt to be sensitive to petrolatum. In the third patient, aggravation was considered to be the result of primary irritation by an ointment during an acute phase of the dermatitis.

One patient with severe poison ivy dermatitis showed aggravation and progression of lesions after extensive local application of hydrocortisone in both types of ointment bases. She was hospitalized for ACTH therapy and required considerable bland local treatment as well. Several weeks after the complete subsidence of the dermatitis, patch tests with hydrocortisone and the ointment bases failed to reveal any evidence of specific sensitization. Further, the patient was given the ointments to rub into the skin daily for several weeks without any resulting irritation. It was felt in this instance that the aggravation noted was due to primary irritation by an ointment in an acute phase of a dermatitis which ordinarily would be treated by bland local therapy such as compresses, colloid baths, and shake lotions. A similar situation was felt to exist in a case of acute deep vesicular dermatitis of the hands, classified as pompholyx. Nevertheless, in observing the effects of hydrocortisone ointment in acute as well as in chronic stages of these dermatoses, it appears likely that in some instances the marked anti-inflammatory properties of hydrocortisone may overcome any primary irritating properties of the ointment base.

In the prolonged use of topical hydrocortisone in such chronic, recurrent, dermatoses as considered in this study, resistance to the favorable influence of hydrocortisone appeared to develop in certain patients who were markedly benefited at first. Sometimes, more frequent and intensive application of the greatest ointment concentration was sufficient to again control the dermatitis. In others, the condition became severe enough to require systemic hormone therapy, following which a small maintenance dose of oral or parenteral steroid together with topical hydrocortisone to areas of greatest involvement proved the most satisfactory combination for symptomatic control. Such a combination of local hydrocortisone therapy and systemic administration of steroid hormone was also found effective in certain cases of severe, widespread dermatitis where local therapy alone was not feasible.

COMMENT

There is considerable evidence indicating that hydrocortisone, as well as cortisone and ACTH, suppresses cellular activity and is capable of acting at the mesenchymal level.[1] According to Menkin,[18] compound F suppresses the effect of leukotaxine in increasing capillary permeability as well as the leukocytosis-promoting factor of inflammatory exudates. Deposition of fibrin is reduced, and less fibrinogen seeps out into inflamed areas. All of these effects point to activity at a cellular level, since these factors are liberated by the injured cell. It is very unlikely that the effect produced by local hydrocortisone is related to its absorption from the skin, since the quantity that is effective by topical application, even if completely assimilated through the skin, would hardly approximate the amounts of hormone required for control of the dermatitis by systemic administration.[4] It has also been demonstrated that inunction of large amounts of hydrocortisone acetate into normal and diseased skin fails to induce a fall in circulating eosinophils, suggesting that little, if any, hydrocortisone is absorbed through the skin into the systemic circulation.[19]

While cortisone and hydrocortisone are similar in their major metabolic and therapeutic effects, they differ quantitatively with respect to potency, and in their local effect on tissues. Comparative studies of their physiologic action indicate that hydrocortisone is approximately twice as potent as cortisone when administered by oral or parenteral routes, and even more effective when applied locally.[1] The difference in their clinical effects, however, is much less striking. It has been suggested that since hydrocortisone is probably the principal hormone secreted by the adrenal cortex, it may be possible that cortisone, in order to be therapeutically effective, must first be transformed to hydrocortisone, or that hydrocortisone is more readily converted to an active metabolite than is cortisone.[20] Since hydrocortisone is approximately one-seventh as soluble as cortisone in body fluids, it has also been suggested that this greater insolubility may account for its increased local effectiveness.[7]

The current observations that hydrocortisone ointments are frequently capable of inducing marked remissions in allergic as well as in certain nonallergic dermatoses is in accord with the experience of Sulzberger and coworkers,[3, 4] although one report to the contrary has recently appeared.[21] It is our impression that hydrocortisone is one of the most effective topical agents yet encountered for the symptomatic treatment of eczematous allergic dermatoses. The greatest success in its use is dependent on the understanding that it is not curative in its effect, and that the benefit which may accrue during its use usually disappears rapidly unless the underlying cause of the dermatitis is in some way eliminated or controlled. The necessity for allergic diagnosis and therapy is still of paramount importance in patients with allergic disease.

A proper selection of cases for hydrocortisone ointment therapy appears to be an important factor in the degree of success which may be expected from its use. Extensive dermatitis involving wide areas of skin may be better managed, initially at least, by systemic hormonal therapy, and later perhaps with local hydrocortisone, or with a combination of both.

As already pointed out, certain eruptions are more amenable to the effects of locally applied hormone than others. Deeper cutaneous lesions are not as readily influenced by this mode of treatment since there is apparently very little absorption of the hormone through the superficial layers of the skin. During very acute phases of a dermatitis, initial therapy with bland local measures or systemic therapy may be wiser, since the primary irritating effects of ointment bases may occasionally obviate the favorable influence of topical hydrocortisone.

SUMMARY AND CONCLUSIONS

The topical use of 1 and 2½ per cent hydrocortisone in ointment form was found to exert a profoundly favorable influence on the course of certain eczematous and papulosquamous eruptions, principally those of an allergic nature, confirming the earlier reports of Sulzberger and co-workers.[3, 4] Both the free alcohol of hydrocortisone and hydrocortisone acetate appeared equally effective in this respect. In a series of 159 patients observed during this study,

marked improvement often occurred in a period of twenty-four to forty-eight hours in such conditions as atopic dermatitis, eczematous contact-type dermatitis, chronic eczema of the hands, lichen simplex chronicus, and otitis externa. Improvement in chronic dermatoses was maintained only as long as the ointment was applied, and relapse generally followed within two or three days of cessation of application. Satisfactory control of chronic eruptions for prolonged periods was frequently possible by continued daily application, although tolerance developed in some instances. Certain types of cutaneous lesions were more amenable to the effects of local hydrocortisone than others. The most satisfactory response occurred in excoriated, papulovesicular, scaling, and lichenified lesions. Urticarial and deep vesicular lesions responded least favorably. Very widespread or generalized eruptions usually required systemic treatment as well as local measures for satisfactory control. A 2½ per cent concentration of hydrocortisone was more uniformly effective than a 1 per cent ointment. In some cases, especially atopic dermatitis in younger individuals, the 1 per cent concentration often produced an equally favorable response. Maintenance therapy with the 1 per cent ointment was sometimes possible after initial improvement was induced by the more concentrated preparation. The addition of 0.5 per cent neomycin to hydrocortisone ointment proved particularly effective in the control of secondarily impetiginized eruptions, and in certain cases of otitis externa. Specific sensitivity to hydrocortisone or neomycin did not occur in any of the patients treated, although 9 patients were aggravated by the ointment bases used to incorporate the active materials. The greater local effectiveness of hydrocortisone on the skin, as compared to cortisone, may represent only a quantitative difference, or is perhaps related to the greater insolubility of hydrocortisone in body fluids. More fundamental differences in action have also been suggested. It is felt that hydrocortisone is one of the most effective topical agents yet encountered for the symptomatic treatment of eczematous allergic dermatoses. It has no curative action in these conditions, however, and the necessity for allergic diagnosis and therapy is still of paramount importance in the proper management of such patients.

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ATMOSPHERIC MOLD SPORES IN AND OUT OF DOORS

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SINCE the early days of studies in allergy to mold spores there has been among allergists considerable doubt concerning the relative importance of the indoor and outdoor air as a source of mold spores which can give rise to respiratory allergy. In several of the earliest published cases of mold allergy the source of the mold was attributed to the patient's home.[1-3] Such cases supported the then prevailing impression that allergy to mold spores was a rarity and was confined to individuals with a peculiar residential or occupational exposure. This view was not seriously contested until Feinberg[4] pointed out that in his clinic allergy to mold spores was by no means rare and[5] that the ordinary outside air was a widespread and potent source of exposure to mold spores.

As a result of Feinberg's work, studies on the incidence of mold spores in the air were begun in many places in the United States of America and in other countries. Usually investigations were made in the open air only. Several allergists, however, have emphasized the importance of making studies of the spore content of the air indoors, and more than a few such investigations have now been made. From purely botanical considerations Saito,[6] Rostrup,[7] and Peyronel[8] had investigated the mold content of the air indoors before the question of mold allergy arose. Under the stimulus of mold allergy Prince and Morrow[9]; Rennerfelt[10]; Nilsby[11, 12]; Flensborg and Samsoe-Jensen[13]; Alemany-Vall[14]; Wallace, Weaver, and Scherago[15]; Maunsell[16, 17]; and Swaebly and Christensen[18] have since carried out similar investigations.

Few of the previous investigations, however, took into account the possibility of seasonal variation in the mold spore content of indoor air, and rarely has an investigation of the air indoors been coupled with a similar investigation outdoors to allow a comparison of the two to be made.

The aim of the study which is described here was to obtain information on the relative importance as a source of exposure to mold spores of the air indoors and outside. The main thesis of this paper is concerned with the normal house, but it may be appropriate to include here a note on the abnormal damp house which itself is known to be a source of mold.

The Damp House.—There can be little doubt that in a house which is visibly moldy (i.e., where molds can be observed growing on, e.g., distempered walls, wallpaper, books, leather articles, or textiles) the residents are exposed to higher concentrations of mold spores than the residents of a normal, clean, dry house. Nilsby[11, 12] exposed plates inside several hygienic and unhygienic homes and found that the average number of colonies which developed on a 9 cm. Petri dish exposed for fifteen minutes was 5 in the dry hygienic homes

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but was 55 in homes about which complaints had been made to the Bureau of Health. In several homes in Cardiff, I have examined the molds growing on damp wallpaper, distemper, linoleum, books, etc., by direct microscopic examination and by making from each area of moldy surface many isolations on culture plates. The platinum wire used for making isolations was flame sterilized between successive samplings. The molds most commonly found growing indoors in such situations were *Alternaria tenuis, Aspergillus niger, Aspergillus glaucus, Aspergillus fumigatus, Cephalosporium acremonium, Cladosporium herbarum,* several *Penicillium* species and *Pullularia pullulans.* It is difficult to say which among these species are commoner than the others. Several other species of the common saprophytes occur occasionally. Balfour-Browne[19] and Smith[20, 21] have both described new species of molds found growing on damp walls indoors. The molds growing in dark patches on walls and elsewhere indoors in Israel were found by Kessler[22] to be identically the same as those which he caught most frequently from the air outdoors.

The predominance of a certain species or groups of molds at any particular indoor site would appear to be determined by properties of the immediate environment. Mold growths on damp walls in one house may be different in constitution from apparently similar growths in another house, and the variation can extend to two rooms in the same house. In one room with damp walls which I examined, many isolations from the wallpaper over an area of 1 to 2 square meters produced *Cladosporium* colonies only, while isolations from a similar area on an abutting wall produced mainly *Penicillium* together with some *Cladosporium* and *Aspergillus.* These moldy areas must be produced by the germination and growth of mold spores deposited on the surface from the air. The composition of any particular area of mold might be subsequently fixed by the initial fortuitous deposition alone, but it is also more than possible that within each mold-colonized area (or mold community) there may occur in a certain time a distinct ecological succession of mold species.

The Normal House.—A house which appeared to be a normal, dry, clean dwelling, and not itself a source of molds, was used for this investigation in which a pair of 9 cm. Petri dishes containing Sabouraud's (maltose) agar* were exposed in a bedroom on every weekday for twelve months. The house was adjacent to the hospital and on the same elevation (approximately 25 feet altitude). It was over 60 years old, of stone construction, in good repair and can be considered typical of a large number of houses in Britain. The bedroom where the Petri dishes were exposed was situated on the upper of the two floors. It connected with the remainder of the house through one door, and with the outside through a window (which was never opened during the twelve months of the experiment) and a chimney. No fires were lit in the bedroom during these twelve months. The occupant of the bedroom vacated this room each morning at about 8.30 A.M. and it was left undisturbed until the technician

*This medium was used for the sake of continuity and comparability of results with the previous investigations of Hyde and Williams.[32] They had earlier, in a long series of Petri dish exposures, compared this medium with others such as potato-dextrose agar and glucose-peptone agar, and had found the mold catches on the several media to be closely similar.[32] In view of these results Sabouraud's agar was chosen as the standard medium because of the simplicity of preparation of uniform successive batches of medium.

arrived bringing the Petri dishes. The dishes were taken into the bedroom, placed on the bed and at 10 A.M. uncovered with as little disturbance as possible. The technician then quietly left the room, later returning in time to recover the plates after an exposure of ten minutes by stop watch.

At the same time on every weekday a similar pair of plates were exposed for ten minutes in a Hyde and Williams[23] shelter situated on a lawn in the hospital grounds. This outdoor site was some 60 yards away in a straight line from the house.

To prevent the inclusion in the count of any laboratory contaminant, all plates were poured and sealed with adhesive paper at least five days before their exposure. After exposure the plates were again sealed and incubated at room temperature for five days after which the mold colonies which had grown were identified and recorded. Those colonies which bore no spores at the first observations were re-examined after further incubation. Where a mold colony proved difficult to identify accurately on the original plate, subcultures were made on slides and on plates of other media, e.g., malt agar, and Czapek-Dox + yeast agar.[24] Colonies which finally failed to produce spores were labeled *Mycelia sterilia.* For convenience this large and diverse group was subdivided by means of the color characteristics of mycelium into three sections—(a) entirely white mycelium, (b) white mycelium above, dark beneath or reverse, and (c) entirely dark-colored mycelium. In practice this classification, though arbitrary, brought together colonies of broadly similar morphologic and cultural characters. The group *Mycelia sterilia* (white) contained many *Oospora*-like colonies and several others resembling Basidiomycetes mycelia. The *Mycelia sterilia* (white and dark) included a large proportion of colonies closely resembling (in mycelial characteristics) nonsporing or poorly sporing colonies of *Alternaria* and several others resembling Basidiomycetes mycelia. The *Mycelia sterilia* (dark) were a small group without marked affinities.

RESULTS

During the whole year 626 Petri dishes were exposed as described at each site. The total mold catches in the bedroom and in the open air are shown separately in Table I. The main results were:

1. The outdoor catch was more than five times as large as the indoor catch.

2. The same molds were caught indoors as outside and they were caught in approximately similar proportions at both sites. (Fig. 1.)

3. Taking the year as a whole the mold caught in greatest numbers, both indoors and out, was *Cladosporium* followed by sterile mycelia and *Penicillium.*

4. Eight genera *(Cladosporium, Penicillium, Pullularia, Aspergillus, Phoma, Botrytis, Epicoccum* and *Oospora)* together with the sterile mycelia made up more than nine-tenths of the total catch at each site.

5. From June to October at both sites *Cladosporium* was by far the most prevalent mold, but during the rest of the year, when the numbers of *Cladosporium* were much lower, *Penicillium* predominated. *Penicillium* shows little variation in incidence throughout the year (Fig. 2).

TABLE I. ANALYSIS OF THE MOLD COLONIES RESULTING FROM THE DAILY EXPOSURE OF TWO CULTURE PLATES THROUGHOUT ONE YEAR

THE OUTDOOR CATCH			THE INDOOR CATCH		
GENUS OR GROUP	COLONIES CAUGHT ON 626 PLATES	PER CENT OF ALL COLONIES	GENUS OR GROUP	COLONIES CAUGHT ON 626 PLATES	PER CENT OF ALL COLONIES
Cladosporium	3,097	45.2	Cladosporium	463	35.9
Mycelia sterilia (white)	821	12.0	Mycelia sterilia (white)	293	22.7
Penicillium	668	9.7	Penicillium	194	15.1
Pullularia	588	8.6	Oospora	71	5.5
Mycelia sterilia (white & dark)	250	3.6	Aspergillus	53	4.1
			Mycelia sterilia (dark)	30	2.3
Aspergillus	204	3.0	Botrytis	29	2.2
Phoma	199	2.9	Mycelia sterilia (white & dark)	26	2.0
Botrytis	160	2.3			
Epicoccum	152	2.2	Pullularia	25	1.9
Oospora	144	2.1	Sporotrichum	24	1.9
Candida	113	1.6	Candida	14	1.1
Sporotrichum	105	1.5	Epicoccum	9	0.7
Mycelia sterilia (dark)	100	1.5	Monilia	9	0.7
Alternaria	44	0.6	Torula	9	0.7
Other genera	214	3.1	Other genera	40	3.1
	6,859			1,289	

THE OTHER GENERA CAUGHT, INDIVIDUALLY COMPOSING LESS THAN 0.5 PER CENT OF THE TOTAL CATCH

THE OUTDOOR CATCH				THE INDOOR CATCH	
	COLONIES CAUGHT ON 626 PLATES		COLONIES CAUGHT ON 626 PLATES		COLONIES CAUGHT ON 626 PLATES
Cephalosporium	30	Scopulariopsis	2	Phoma	6
Mucor	29	Trichosporium	2	Fusarium	5
Torula	25	Verticillium	2	Mucor	5
Mycelia sterilia (dark)	25	Acrostalagmus	1	Cephalosporium	4
Monilia	21	Allantospora	1	Rhizopus	4
Stemphylium	14	Botryotrichum	1	Trichothecium	3
Fusarium	9	Chaetomium	1	Heterobasidiom	2
Trichoderma	8	Diplodia	1	Trichosporium	2
Trichothecium	8	Gliomastix	1	Acremonium	1
Rhizopus	6	Myxomycete	1	Allantospora	1
Heterobasidion	5	Spicaria	1	Diplodia	1
Diplococcium	4	Spondylocladium	1	Paecilomyces	1
Gliobotrys	4	Stysanus	1	Papularia	1
Ciboria	3	Synsporium	1	Stysanus	1
Paecilomyces	2	Tilachlidium	1	Unidentified	3
Papularia	2	Trichocladium	1		

6. No mold occurred more frequently on the indoor plates than it did on the outdoor plates.

The variation (among the predominant genera) of the ratio of the outdoor catch to the indoor catch is shown in Table II. This ratio varies from 2.3 *(Oospora)* to 33.2 *(Phoma)* and ∞ *(Alternaria)*. Some explanation of this variation is attempted later.

The effect of season on the catches of the commoner molds is shown in Table III and Fig. 2. In the summer months *Cladosporium, Botrytis, Epicoccum,* and *Pullularia* occur on the outdoor plates in numbers which are strikingly

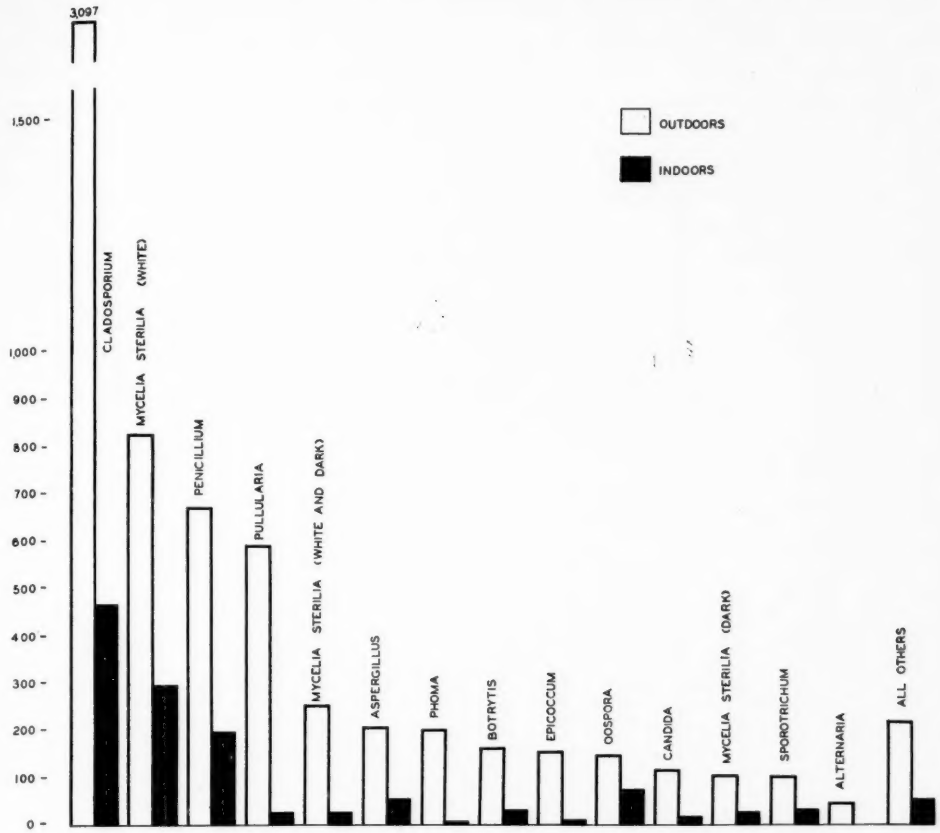

Fig 1.—The relative prevalence of the chief molds caught indoors and outside during the year April, 1951 to March, 1952.

TABLE II. THE RELATIONSHIP BETWEEN THE INDOOR AND OUTDOOR CATCHES

	OUTDOOR CATCH	INDOOR CATCH	OUTDOOR / INDOOR
Cladosporium	3097	463	6.7
Mycelia sterilia (white)	821	293	2.8
Penicillium	668	194	3.4
Pullularia	588	25	23.5
Mycelia sterilia (white and dark)	250	26	9.6
Aspergillus	204	53	3.8
Phoma	199	6	33.2
Botrytis	160	29	5.5
Epicoccum	152	9	16.9
Oospora	144	71	2.3
Candida	113	14	8.1
Sporotrichum	105	24	4.2
Mycelia sterilia (dark)	100	30	3.3
Alternaria	44	—	∞
Total catches	6859	1289	5.5

higher than in the winter months. This seasonal incidence is equally well shown in the indoor catches. Similarly, the groups *Mycelia sterilia* (white) and (white and dark) also have a higher incidence in summer on the outdoor and indoor plates. *Aspergillus* and *Oospora* are the only two genera to show out of doors

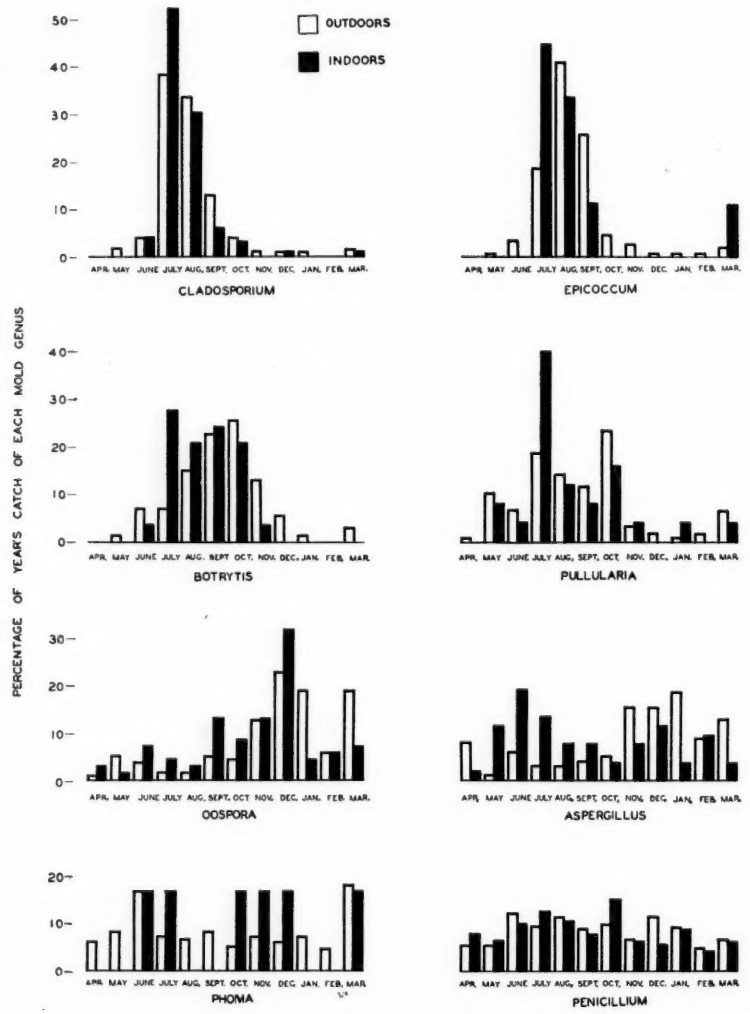

Fig. 2.—Seasonal variation in incidence of the commonest air-borne molds. The histograms show the percentage occurring in each month of the year's catch of each mold genus.

a higher incidence in the winter months. In the case of *Oospora* the higher winter incidence is reflected in the indoor catch, but that of *Aspergillus* is not. The reason for this difference is not clear.

The very large seasonal variation in numbers of *Cladosporium* colonies is shown in Fig. 3. The weekly catch (i.e., the total number of colonies on six successive daily pairs of plates) varies from 0 to 1 during February to April,

indoors and outside, to the highest catches of 440 colonies outdoors and 80 colonies indoors at the end of July. The correspondence between the outdoor and indoor catches is marked and the graph indicates that the indoor catch is merely a diminished reflection of the outdoor catch.

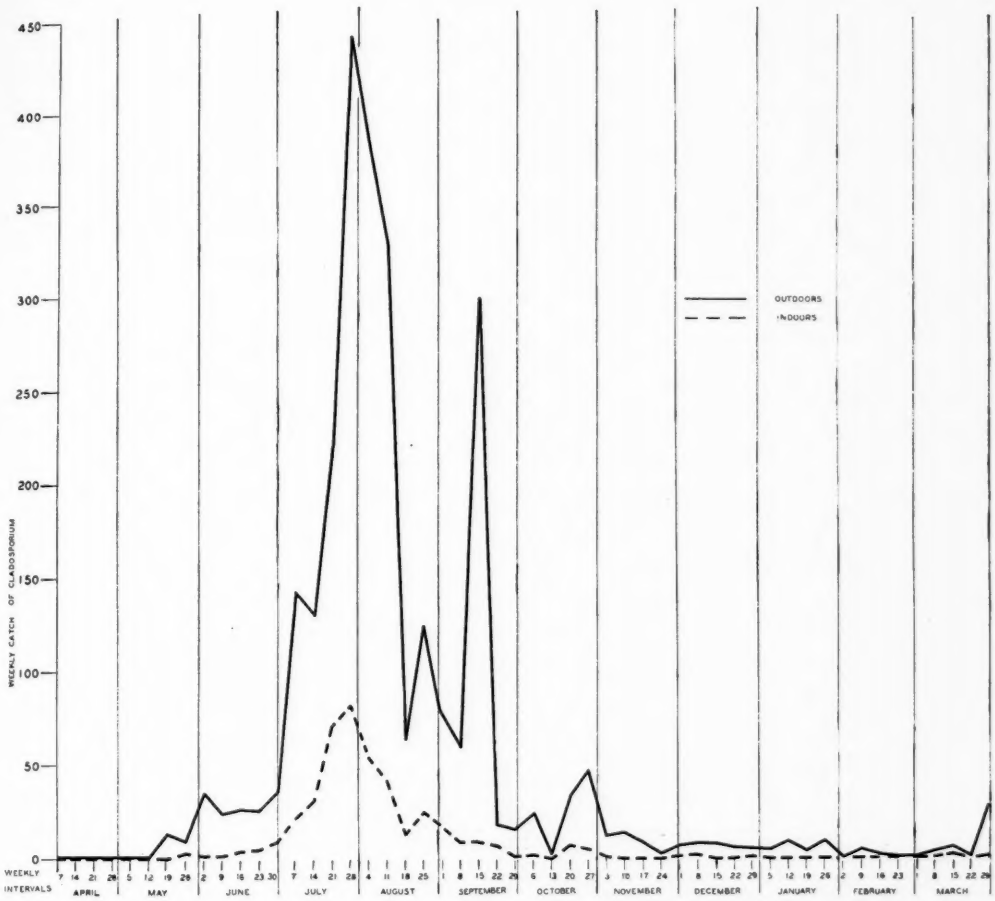

Fig. 3.—The seasonal variation in *Cladosporium* incidence. The graph is plotted at weekly intervals, each point representing the *Cladosporium* catch on six successive daily pairs of plates.

DISCUSSION

The variation from one genus to another in the ratio outdoor catch/indoor catch (Table II) indicates clearly that the factors governing the size of the mold catch are not the same both indoors and outside for all molds. The following remarks are offered as a possible partial explanation of the variation.

1. *Genera with large spores,* e.g., *Alternaria* and *Epicoccum* are known to sediment out of still air more swiftly than smaller spores. [Calculations based on Stokes's Law give the following (approximate) speeds of fall under gravity (terminal velocity) for smooth spherical bodies assuming unit density. A

TABLE III. THE EFFECT OF SEASON ON THE INDOOR AND OUTDOOR CATCHES OF THE COMMONER MOLDS

GENUS OR GROUP	OUTDOOR OR INDOOR	APRIL (25)*	MAY (27)	JUNE (26)	JULY (26)	AUG. (27)	SEPT. (25)	OCT. (27)	NOV. (26)	DEC. (26)	JAN. (27)	FEB. (25)	MAR. (26)
Cladosporium	Outdoor	2	54	152	1185	1037	400	120	38	28	27	10	44
	Indoor	1	4	23	242	140	28	15	0	4	1	0	5
Mycelia sterilia (white)	Outdoor	24	66	72	56	142	140	41	115	43	46	20	56
	Indoor	3	18	20	41	69	84	10	17	15	8	2	6
Penicillium	Outdoor	34	35	80	62	75	59	65	44	76	61	32	45
	Indoor	15	12	19	24	20	15	29	12	11	17	8	12
Pullularia	Outdoor	5	60	40	110	83	68	137	20	11	5	10	39
	Indoor	0	2	1	10	3	2	4	1	0	1	0	1
Mycelia sterilia (white and dark)	Outdoor	7	12	15	38	62	37	22	14	14	7	3	19
	Indoor	0	0	2	3	12	3	3	2	0	0	0	1
Aspergillus	Outdoor	16	2	12	6	6	8	10	31	31	38	18	26
	Indoor	1	6	10	7	4	4	2	4	6	2	5	2
Phoma	Outdoor	12	16	33	14	13	16	10	14	12	14	9	36
	Indoor	0	0	1	1	0	0	1	1	1	0	0	1
Botrytis	Outdoor	0	2	11	11	24	36	41	19	9	2	0	5
	Indoor	0	0	1	8	6	7	6	1	0	0	0	0
Epicoccum	Outdoor	0	1	5	28	62	39	7	4	1	1	1	3
	Indoor	0	0	0	4	3	1	0	0	0	0	0	1
Oospora	Outdoor	1	7	5	2	2	7	6	18	34	27	8	27
	Indoor	2	1	5	3	2	9	6	9	22	3	4	5
Total mold catch	Outdoor	117	309	496	1571	1562	846	497	349	313	284	150	365
	Indoor	22	48	93	360	271	171	87	57	75	40	27	38

*Number of daily pairs of Petri dishes contributing to the stated number of mold colonies.

sphere of 25 μ diameter (the order of size of the larger mold spores), terminal velocity—1.9 cm. per second, and a sphere of 5 μ diameter (the order of size of the smaller mold spores), terminal velocity—0.07 cm. per second]. Since the bedroom was undisturbed for about one and one-half hours before the Petri dishes were exposed, it is likely that most of the larger spores had settled out of the air. If, as is believed on morphologic grounds, a proportion of the *Mycelia sterilia* (white and dark) consists of nonsporing *Alternaria* colonies, then the same explanation fits the high outdoor/indoor ratio for this group.

2. *Genera with moist spores,* e.g., *Phoma, Pullularia,* and *Candida,* are frequently found in relatively higher numbers on our plates exposed outdoors in rainy weather. This probably increased the outdoor catch relative to the indoor catch of this type of mold spore.

3. *Genera with small spores,* e.g., *Penicillium, Aspergillus, Oospora,* and *Sporotrichum.* In air moving at low wind-speeds spores are caught on 'surface-traps' (e.g., Petri dishes) with a lower efficiency than in still air.[25] This effect becomes more pronounced the smaller the mass of the spore. During sampling, conditions in the bedroom were very still in contrast to the more or less constantly moving air outdoors, and it may be that the small spores were trapped relatively more efficiently indoors, resulting in a lower outdoor/indoor ratio.

PREVIOUS INVESTIGATIONS.—The first attempt at investigating the mold content of the air indoors appears to have been made by Saito[6] in Japan. He exposed a total of 24 plates in an operating theater, a cloakroom, and a lecture room in conjunction with a longer series of outdoor exposures. Indoors he recorded mainly *Cladosporium* and *Penicillium.* Rostrup[7] in Denmark exposed plates in

the same house at irregular intervals over a period of one year and found *Penicillium* commonest followed by *Cladosporium* (showing higher incidence in summer) and *Pullularia*. In Italy, Peyronel[8] found *Penicillium* and *Mucor* the most frequent indoor molds. Prince and Morrow[9] in Texas caught from the air indoors as many mold spores as they caught out of doors, and in spring the numbers caught indoors were even higher than those outside. Rennerfelt[10] in Sweden found fewer molds in indoor air than outside. On the indoor plates *Penicillium* predominated followed by *Cladosporium*. In the same country Nilsby[11, 12] found that *Penicillium*, *Cladosporium*, and *Aspergillus* predominated indoors, but this conclusion was based upon an aggregate of some exposures made in dry hygienic houses and others made in unhygienic moldy houses. Flensborg and Samsoe-Jensen[13] in Copenhagen found *Penicillium*, *Aspergillus*, *Cladosporium*, and *Pullularia* predominating on their indoor plates, but 19 exposures only were made—none in the summer months. In Barcelona, Alemany-Vall[14] found that the commonest mold in indoor air was *Penicillium* followed by *Cladosporium*, *Alternaria*, and *Aspergillus*. Wallace, Weaver, and Scherago[15] reported that *Penicillium* and *Aspergillus* were the predominant molds in indoor air in Kentucky in the United States of America. They found no *Cladosporium* (either indoors or outside) which is surprising in view of the several reports[26-31] which indicate that high numbers of *Cladosporium* occur in the air perennially in the southern portion of the United States. In London, Maunsell[16] using the slit sampler technique found fewer molds in the air in undisturbed rooms than outside. Later[17] the same author showed how the catch of molds on agar plates was considerably increased during and after sweeping and dusting operations. Swaebly and Christensen[18] exposed plates at various times of day in fifteen houses in Minnesota during early spring and summer, and also exposed plates out of doors at the same locations. They found that the indoor counts were lower than outdoors but generally, whereas *Penicillium* and *Aspergillus* predominated indoors, *Alternaria* and *Cladosporium* were predominant outside. One-quarter of their exposures, however, were made after sweeping had been carried on, and, as these exposures showed considerably higher mold catches than the others, they will have seriously influenced the indoor results as a whole. This may have been the cause of the difference between the indoor and outdoor results.

Among the aforementioned investigations, in one alone[15] were regular (but not frequent) observations extended over as long as one year. The majority consisted of a relatively small number of exposures carried out at irregular intervals and it is probable that their results do not reflect the precise order of predominance of the molds in the indoor air throughout the year, nor in particular, during the summer months. Most authors, however, are in substantial agreement in finding lower concentrations of molds in the air indoors, and in naming as the four commonest genera in indoor air *Aspergillus*, *Cladosporium*, *Penicillium*, and *Pullularia*. These four genera are usually (except in the areas where *Alternaria* predominates) the commonest molds in the air outdoors.

SUMMARY AND CONCLUSIONS

In houses which are observably moldy, the mold spore content of the air may be different in constitution (as well as in quantity) from that of the outside air. Culture experiments show that the molds growing in such houses are usually the common atmospheric contaminants, though the predominant species can and does vary from one house to another.

Daily exposures of Petri dishes throughout one year showed that in a normal, dry, fairly old house, the air contains the same molds (though in lower concentrations) as the air outside. The indoor catch fluctuates seasonally in size and constitution parallel with the seasonal fluctuations in the outdoor catch.

The botanical findings indicate that in the normal house the most important source of air-borne mold spores is the outside air; that indoors relatively few spores are produced and released into the air. This suggests that in the investigation, diagnosis, and treatment of allergy to air-borne mold spores the most important prerequisite is a thorough understanding of the mold spore content of the air out of doors.

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THE EFFECT OF SOME SYMPATHICOMIMETIC AMINES AND ENZYME BLOCKING AGENTS ON ASTHMA IN THE GUINEA PIG INDUCED BY ANTIGEN OR HISTAMINE AEROSOLS*

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VARIATION in the amounts of endogenous epinephrine has been used from time to time as an explanation of the varying degree of anaphylactic reactivity of the experimental animal and the fluctuations of intensity of allergic manifestations in man. Since monoamine oxidase is responsible for part of the degradation of epinephrine, a substance which inhibits the action of this enzyme would be expected to make a greater amount of active endogenous or exogenous epinephrine available. By such a study, one might get a clue as to the possible role of endogenous epinephrine in anaphylaxis and allergy. The successful outcome of such an investigation might also result in the addition of a new agent in the treatment of allergy.

Since 1-isonicotinyl-2-isopropyl hydrazine (iproniazid or Marsilid) had been shown to inhibit monoamine oxidase almost completely in rats and guinea pigs, it seemed of interest to investigate the action of this drug in anaphylaxis. In a previous communication,[1] we showed that the inhibition by this drug did not affect the response of the sensitized animal to the challenge of antigen application or to histamine.

The purpose of the present study was to observe the effect of two other antituberculous drugs with known enzyme blocking activity, isonicotinic acid hydrazide (isoniazid) and pyruvic acid isonicotinoyl hydrazone, on anaphylaxis and histamine response in the guinea pig. We also studied the anti-anaphylactic action of other amines, such as phenylethylamine, Tyramine, ephedrine, Benadryl, and amylamine.

PROCEDURE

Female guinea pigs of varying weights (average 400 grams) were utilized. The antigen-antibody reaction was investigated in only one group. All other groups were challenged by exposure to histamine aerosol. In the group in which anaphylactic reactions were studied the animals were sensitized passively by an intravenous injection of 2 ml. of antiovalbumin guinea pig serum and then exposed after forty-eight hours to an aerosol of 0.2 per cent solution of twice crystallized ovalbumin. All other guinea pigs were exposed to an aerosol of histamine derived from solutions of either 0.5 mg. per milliliter or

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TABLE I. THE EFFECT OF EPINEPHRINE AND EPHEDRINE AND ENZYME BLOCKING AGENTS ON THE SPEED OF ONSET OF ASTHMA INDUCED BY AEROSOLS OF HISTAMINE

NO. ANIMALS	AEROSOL	DRUG INVESTIGATED	AVERAGE TIME REQUIRED BEFORE REACTION				
			1+	2+	3+	4+	DEAD
10	Histamine 0.5 mg./ml.	Iproniazid		58″			
3	Controls			1′48″			
7	Histamine 0.25 mg./ml.	Iproniazid		3′58″			
12	Controls			2′11″			
10	Histamine 0.25 mg./ml.	Isoniazid		2′23″			
3	Controls			2′15″			
5	Histamine 0.25 mg./ml.	Pyruvic acid Isonicotinoyl hydrazone		5′			
4	Controls			56″			
5	Histamine 0.25 mg./ml.	Ephedrine 10 mg./L. pig by aerosol 15′ before challenge		2′48″			
3	Histamine 0.25 mg./ml.	Ephedrine 10 mg./L. pig by aerosol 30′ before challenge		1′30″			
3	Controls			1′37″			
5	Histamine 0.25 mg./ml.	Epinephrine 0.4 ml. 1:1,000/L. pig by aerosol 30′ before challenge		3′12″			
3	Controls			1′48″			
6	Histamine 0.25 mg./ml.	Epinephrine 1:100 by aerosol for 10′ – 30′ before challenge				3′46″	
5	Histamine 0.25 mg./ml.	Epinephrine 1:100 by aerosol for 10′ – 15′ before challenge				3′16″	
3	Controls			2′40″		3′55″	

0.25 mg. per milliliter. The end point of induced asthma both in the antigen- and histamine-treated animals was the same as previously described by us.[1] Epinephrine was administered only by aerosol, ephedrine was administered both by aerosol and intraperitoneally, while all other drugs were given intraperitoneally. Iproniazid (Marsilid) and isoniazid (Rimifon) were injected in doses of 50 mg. per kilogram of body weight, and pyruvic acid isonicotinoyl hydrazine in doses of 100 mg. per kilogram of body weight, two hours before challenge. The amines were administered in varied doses fifteen to twenty minutes before challenge.

RESULTS

1. *Effect of Antituberculous Drugs and of Aerosolized Ephedrine and Epinephrine on Histamine-Induced Asthma.*—As is evident from Table I, asthma induced by aerosols of histamine obtained from solutions of 0.5 or 0.25 mg. per milliliter occurred in approximately the same time in the control series as in those treated with iproniazid. Isoniazid likewise did not protect the guinea pigs exposed to histamine aerosol. Pyruvic acid isonicotinoyl hydra-

zone, however, gave considerable protection; the treated animals tolerated the aerosol about 5 times as long as those not treated. Ephedrine, given by aerosol fifteen or thirty minutes prior to an exposure to an aerosol of histamine, failed to influence the pattern of the asthma.

The pretreatment of the guinea pigs with epinephrine aerosol in concentrations of 1:1,000 or 1:100 gave little or no protection. As a matter of fact, those animals treated with epinephrine aerosol 1:100 experienced convulsions from the histamine aerosol earlier than the control series.

2. *Phenylethylamine in Asthma From Antigen Aerosol.*—Large, as well as small, doses of phenylethylamine gave no protection against asthma produced by an antigen aerosol (Table II). The average reaction time of 3 minutes, 20 seconds to the aerosol is not significantly different from that of 2 minutes, 30 seconds for the controls. The application of phenylethylamine to animals pretreated with iproniazid also gave no protection.

TABLE II. THE EFFECT OF PHENYLETHYLAMINE AND IPRONIAZID ON THE SPEED OF ONSET OF ASTHMA INDUCED BY AN AEROSOL OF OVALBUMIN

NO. ANIMALS	PHENYLETHYLAMINE MG. INTRAPERITONEALLY	IPRONIAZID	AVERAGE TIME REQUIRED BEFORE REACTION			
			1+	2+	3+	4+
1	1		2′			
4	5				3′37″	
1	6				4′	
2	6	×			1′30″	
3	10				2′50″	
1	15				3′30″	
3	20				2′45″	
Controls						
4					2′30″	

3. *The Effect of the Amines on the Histamine-Induced Asthma.*—

a. Phenylethylamine, in doses of 1 to 10 mg. intraperitoneally, failed to give protection. In large toxic doses (30 mg. and up) some of the animals showed significant protection against asthma induced by histamine aerosol.

b. Amylamine, in varying doses with or without pretreatment with iproniazid, failed to influence the asthma produced by the histamine aerosol.

c. Tyramine produced results identical with those obtained from amylamine.

d. Ephedrine given intraperitoneally, in contrast to aerosol, in doses just below those that produce the first mild toxic effect, gave a significant protection. Smaller doses seem to give a lesser protection. Isoniazid appeared to diminish the protective effect of ephedrine, while iproniazid had no influence in either direction.

e. Iproniazid did not increase the tolerance time of guinea pigs to histamine aerosol when combined with doses of Benadryl moderately less than those required to protect the guinea pig. The previously mentioned findings are illustrated in Tables II and III.

TABLE III. THE EFFECT OF OTHER AMINES, ENZYME BLOCKING AGENTS, AND BENADRYL ON SPEED OF ONSET OF ASTHMA INDUCED BY AEROSOLS OF HISTAMINE 0.5 MG./ML.

NO. ANIMALS	I.P. (MG.)	INFUSION (MG.)	IPRONIAZID	AVERAGE TIME REQUIRED BEFORE REACTION					
				0	1+	2+	3+	4+	DEAD
	Phenylethylamine								
2	1						1′52″		
1	1.5						2′		
4	2						1′55″		
1	4						3′20″		
1	6						2′30″		
3	10						2′41″		
2	30			10′				5′	1
1	50						10′		
4		50					4′35″		
1	60				7′				30′ in chamber
1	1		×				35″		
2	5		×				3′30″		
1	10		×			7′			
1	15		×		8′				
Controls									
4							2′30″		
	Amylamine								
1	5						1′		
1	10						2′		
1	20						2′30″		
4		25					2′12″		
2	40						2′45″		
1	5		×				1′30″		
1	10		×				2′		
1	20		×				3′35″		
2	50		×				2′17″		
	Tyramine								
1	10						2′		
3	20						2′10″		
1	40						3′		
1	10		×				2′20″		
3	20		×				2′43″		
1	40		×				3′20″		
Controls									
3							2′18″		
	Ephedrine								
1	2						1′30″		
4	3						5′		
2	5						4′30″		
13	10						7′22″		
2	3		×				10′		
3	5		×				8′13″		
3	10		×				7′30″		
1	12		×				6′		
2	20		×				10′		
1	40		×				10′		
1	60		×				10′		
5	10		Isoniazid				2′29″		
Controls									
5							1′52″		
	Benadryl		Ipronia-zid						
6	7						6′38″		
8	7		×				6′51″		
Controls									
5							2′5″		

I.P. = Intraperitoneally.

DISCUSSION

Monoamine oxidase[2] destroys sympathicomimetic amines, such as epinephrine and phenylethylamine, while diamine oxidase inactivates histamine, among other substrates. The two enzymes, therefore, may play a role in the response of the animal organism to biologically active amines which are either administered from the outside or liberated from within. The more active these enzymes are, the lower the amine level and the smaller the response will be. Since it is possible to inhibit selectively the two enzymes in vivo, the monoamine oxidase by iproniazid,[3] the diamine oxidase by isoniazid,[4, 5] this possible function of these enzymes can be tested with the help of these drugs.

Our present study shows that the anaphylaxis in guinea pigs is not altered by iproniazid nor by isoniazid. The data with iproniazid confirm previous results.[1] We must, therefore, conclude that the two amine oxidases are not limiting agents under the conditions of our experiment. The moderate protection provided by pyruvic acid isonicotinoyl hydrazone deserves attention. Since this drug exerts little inhibitory action on both enzymes,[6] other systems than the two enzymes must be affected by it.

It has been shown[7] that guinea pigs pretreated with Benadryl are fully protected against asthma induced by histamine aerosol. The drug inhibits monoamine oxidase,[8] but to a much lesser degree than iproniazid. If the action on monoamine oxidase would contribute essentially to the pharmacologic function of the drug, iproniazid should potentiate its action. The negative outcome of the result (Table III) again indicates that monoamine oxidase is not the limiting factor in our system.

It is of some interest to note that the sympathicomimetic amines, including phenylethylamine, Tyramine, and amylamine, do not protect the guinea pig in anaphylaxis, even in the presence of iproniazid, which prevents effectively[3, 9, 10, 11] the degradation of these amines. Thus the possibility is clearly ruled out that these amines fail to act because they are destroyed too fast within the animal. High doses of phenylethylamine, however, seem to have some protective function against histamine which is potentiated by iproniazid, indicating that monoamine oxidase is a limiting factor here.

The discrepancy between clinical efficiency of epinephrine and its ineffectiveness in our animal experiment deserves attention. Lack of protection by ephedrine and epinephrine aerosol might be explained by such factors as differences in absorption between guinea pigs and man or the detrimental effects from small doses previously noted.[1] Ephedrine given by injection produces moderate protection against histamine asthma, but a large dose must be administered.

As stated previously, guinea pigs pretreated with Benadryl are protected against asthma induced by histamine aerosol. Both Benadryl and iproniazid inhibit monoamine oxidase. One might expect a synergism in the antianaphylactic action of the two drugs by the potentiation of endogenous epinephrine by both and the antihistaminic action of Benadryl. The result was a negative one. We are not able to explain the protection obtained by pyruvic acid isonicotinoyl hydrazone.

Since the sympathicomimetic amines, phenylethylamine, Tyramine, and amylamine, which are substrates of monoamine oxidase, do not play an essentially protective role in anaphylaxis and since the complete inhibition of monoamine oxidase by iproniazid does not protect the guinea pig, our previous observations[1] concerning the specific action of epinephrine can be supported. On the other hand, ephedrine, which is not a substrate for monoamine oxidase,[2] gives a relative protection when administered intraperitoneally.

SUMMARY

1. The inhibition of the epinephrine-destroying enzyme, monoamine oxidase, by iproniazid, thus making more exogenous or endogenous epinephrine available, does not influence the asthma in the guinea pig produced by a histamine aerosol. This confirms our previously reported findings.

2. The inhibition of a histamine-destroying enzyme, diamine oxidase (histaminase), by isoniazid, thus making more exogenous or endogenous histamine available, does not increase the asthma produced in guinea pigs by a histamine aerosol.

3. The antituberculous drug pyruvic acid isonicotinoyl hydrazone, which has little inhibiting action on either monoamine oxidase or diamine oxidase, increased the tolerance of the animals to the histamine aerosol. The mechanism is unexplained.

4. Amines related to epinephrine (phenylethylamine, amylamine, and Tyramine) had no influence on asthma produced by aerosols of histamine or antigen.

5. The pretreatment of the animals with iproniazid, which inhibits the action of monoamine oxidase, destroying these amines more completely than it does epinephrine, failed to affect the influence of the asthma-inducing aerosols.

6. The protection against asthma produced by intraperitoneal injection of ephedrine was not enhanced by pretreatment with iproniazid.

7. Since Benadryl is also a moderate inhibitor of monoamine oxidase, its action in preventing histamine-induced asthma might be explained on that basis. The addition, however, of iproniazid in Benadryl-treated animals failed to potentiate the action of the latter. This supports the belief that the antiallergic action of Benadryl does not depend on monoamine oxidase.

8. The experiments herein described together with those previously reported by us lead to the conclusion that the action of monoamine oxidase cannot be the only mechanism in the prevention of anaphylaxis in the guinea pig.

9. Evidence is presented which indicates that the role of endogenous diamine oxidase (histaminase) in the regulation of histamine shock in the guinea pig is negligible.

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PROPHYLAXIS OF ALLERGIC DISEASE IN THE NEWBORN INFANT

A Reply to Various Critical Comments

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THE published criticisms[2, 8, 11, 12] of our work,[6, 10] on the prophylaxis of allergic disease in the newborn child and in early infancy have, naturally, been of great interest to us. They are very welcome, principally because they will be of assistance in future studies. At the moment, the discussion of these criticisms gives us the opportunity of putting into print some sidelights on our work which, while of considerable significance, we did not think of sufficient importance to include in our original publications.

These studies were begun about twenty years ago when one of us (J. G.) was greatly impressed by the suffering of infants with severe eczema, the anguish such an infant could cause in a family, and the consequent reluctance of the parents of such a child, particularly when the first-born, in view of the commonly accepted knowledge of the hereditary nature of allergic disease, to have more children. It was felt that one of the best contributions one could make as a pediatrician was to study what might be done in the way of prophylaxis of allergic disease in the newborn or young infants. It seemed possible that many of the allergic disturbances in this age group were due to cow's milk, which, as was later pointed out,[3] is not a natural food for newborn human infants, as is the common opinion, but was designed by nature for feeding calves. About the time this interest was developed, Hill and Stuart[9] had reported on a commercially available soybean milk* devised by them with which considerable success was experienced in the feeding of infants with eczema. Whether or not one could feed newborn infants from birth on soybean milk was not well established, as this had been done only in the case of one infant by Tso,[13] a Chinese physician.

The reasons for starting a newborn infant on soybean milk in an attempt to prevent the development of allergic disease in the newborn child[5] were explained to a number of pregnant mothers who had had the most bitter experiences with atopic dermatitis in their infants in the past. With great reluctance, some consented to this experiment. The success of the procedures advocated was such that, within a few years, there was no difficulty in persuading the mothers of potentially allergic infants to start their newborn babies on a cow's milk substitute, and eventually we saw many new patients because of this method of feeding. It was soon obvious that controlled studies should be made, despite our clinical impression of the favorable results. It also seemed perfectly evident that sibling controls, rather than alternate cases, would be best for this purpose.

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*Sobee (Mead Johnson & Company).

In a recent letter to the editor of the *Journal of the American Medical Association*[11] and in an editorial in the JOURNAL OF ALLERGY,[12] Lowell and Schiller have critically commented upon our experiments. Their criticisms, for the most part, from the standpoint of theoretical statistics, are valid. We recognized that we had not conducted an ideal experiment, theoretically, in that we did not, in advance, randomly choose which infants were to be in the "experimental group," which were to compose the "sibling control group," and the "nonrelated control group." This we did because, to the best of our knowledge, there was no way to conduct the experiment in a theoretically ideal manner. The situation resembles the state of affairs of investigations designed to show a connection between smoking cigarettes and lung cancer. Such an experiment cannot be carried out ideally in the society in which we live. It might be done in a totalitarian regime like Hitler's or in the Soviet Union. It would be necessary to select randomly, in advance, a city of reasonable size. Children who had never been exposed to cigarette smoke would have to be chosen in a random manner and divided into two groups, one of which would be taught to smoke cigarettes at a certain age and the other would be so policed that they would not smoke cigarettes or be exposed to cigarette smoke. After a given period, say thirty years, both groups would be killed and autopsies would be performed, and, in this manner, one *might* hope to satisfy even the most critical theoretical statistician as to whether or not smoking cigarettes causes lung cancer. The fact that it is not possible for such a problem to be worked out ideally does not mean that all the present investigations, pro and con, with respect to a possible relationship between cigarette smoking and lung cancer should be completely disregarded. Ultimately, such evidence, in one way or another, may be so conclusive that to disregard it would be to reduce the problem to an absurdity.

Lowell and Schiller[12] also commented that the time over which our experiments were carried out is not stated. One of the paragraphs in our article indicates that our infants were followed from a period of three months to ten years, the largest group (45) having been followed from two to five years.

These authors have indicated, in the strongest possible terms, the importance of our findings, if correct. It is, therefore, rather unfair of them to infer that we sought some other group of controls because we had some doubts about the reliability of the sibling control study. If our conclusions have the tremendous significance attached to them by Lowell and Schiller, it is evident that no precaution should be omitted to establish as many varieties of controls as possible. We fully realized this and, therefore, worked out a control group of infants unrelated by blood to our experimental group. This was done by going through our records *serially*, selecting as controls infants with a background similar to our experimental group and followed at least a corresponding period of time. These infants came to our office in a truly random manner, as we did not, in advance, invite the parents to subject their children to our care and, therefore, it seems fair to regard this as random sampling, although at the time we did not think of it as such. If a girl infant in the experimental group had a father with asthma, a mother with hay fever, and a brother with

eczema, it was attempted to find her counterpart in an unrelated family to use as a control. This, as can be imagined, was a task of tremendous proportions. It took eleven months of our spare time to review the records of 4,710 children in 1,215 allergic families. Of this number, 175 children were found suitable for such a control group. The results of the study showed a remarkable correlation between the sibling control group and the unrelated control group. Fifteen per cent of the experimental group were shown to have developed major allergies by the age of 6 years as compared with 64 per cent of the sibling control group and 52 per cent of the nonrelated control group.

Lowell and Schiller also point out what they consider a major contradiction in our conclusions, namely, that of the infants in the experimental group who later developed major allergies, a significant number did so as a result of sensitivity to cow's milk. We have never stated that the omission of cow's milk from the diet of the newborn infant will *permanently* prevent the development of allergy to cow's milk; that would be in contradiction to what is definitely known about food allergy. The comment of Lowell and Schiller does, however, highlight the fact that cow's milk in infancy is an allergen of high sensitization potential, a fact with which internists, such as our critics, could not be expected to be familiar, particularly since it has long been overlooked by the majority of pediatricians.

Our use of the words, "immunological immaturity," has been very properly criticized. This problem, however, is one of semantics. We believe it is an accurate term in the sense in which we have used it. It is true, of course, that some of the immunological processes are highly developed in early life. It is possible, for example, to vaccinate a newborn infant immediately after birth successfully against smallpox. Whether or not the newborn infant is relatively immature as regards ability to react to infection is, however, not germane to this discussion. As far as foods are concerned, the infant also has the ability to react specifically either by developing a protective mechanism so that a food will be tolerated, or an allergic reaction. The term, "immunological immaturity," as we have used it, refers to the fundamental observation that was the starting point of our work; namely, that many infants who cannot tolerate egg at 3 months of age can tolerate this food when it is given at the age of 9 months. This indicates, at least, maturation of the infant as regards tolerance for a specific food. We trust that in the light of this explanation the reader will have no difficulty in understanding, for lack of a better method of expression, the meaning we have attempted to convey.

The comments by Hill,[8] a pediatric allergist who is one of the leading investigators in the study of atopic dermatitis in infancy and childhood, are highly pertinent and practical. Hill, while granting that, if well-tolerated, soybean milk will nourish an infant as well as cow's milk, has pointed out that soybean formulas are likely to cause diarrhea and irritation of the buttocks which, in newborn infants, may become matters of serious concern. Hill's warning is appropriate and timely. The feeding of the newborn infant should be undertaken only by those who are well trained in this respect.

When diarrhea or sore buttocks appeared, however, we endeavored to treat this in the usual manner, but, if unsuccessful, discontinued the soybean preparation. This was, however, necessary in less than 15 per cent of our cases and this includes those infants where intractable colic or emesis also appeared to be due to the soybean feeding. Since our work was submitted for publication, technologic advances have permitted the introduction of a new powdered soybean milk* which we have found well-tolerated by the great majority of infants studied subsequently who were intolerant of the liquid preparation used in our previous investigation.

Hill further commented that, even though it might be a reasonable assumption that allergy to cow's milk in early infancy might be prevented by starting the newborn potentially allergic infant on soybean milk, one would not expect that this would have any influence upon the development of subsequent allergies. It is a priori reasoning that if one does not feed cow's milk to newborn infants, they will not show allergy to cow's milk during this feeding period. Only about 7 per cent of our experimental group developed eczema, as compared with about 30 per cent of the control groups. Thus the incidence of eczema in the control group was about four times as great as in the experimental group, which is interesting in view of the observation previously made by Grulee and Sanford that infants fed exclusively with cow's milk develop eczema seven times more frequently than the exclusively breast fed. Eczema in our experimental group was, of course, due to other factors than cow's milk. Like Hill, we did not feel that preventing the development of allergic manifestations (i.e., allergy to cow's milk) in early infancy could reasonably be expected to inhibit or prevent the development of subsequent allergies. It was, therefore, a genuine surprise when we investigated this phase of our study to find, as stated previously, that only about 15 per cent of our experimental group later developed major allergies during the period of observation, as compared with about 60 per cent of the control groups. This could well be designated serendipity, since, in seeking to find a way to prevent the development of allergic diseases in the newborn infant, the evidence was that the same procedure would have an important influence on inhibiting the development of subsequent allergies. Perhaps we should not have been astonished at this because it is a well-known clinical observation that once an allergic disease appears in a child others commonly follow, as, for example, the well-known colic, eczema, hay fever, and/or asthma complex. It is obvious, of course, that serendipity cannot be taken into consideration in the planning of an experiment, but that by no means invalidates the results of such research.

It is difficult to understand whether Bowen's[1] discussion of our work is intended to be adverse criticism, commendation, or corroboration. Bowen[2] points out that 51 per cent of the individuals of his series of monozygotic twins suffered from allergic disease. In 85 per cent of his cases a family history of allergy was present. The incidence of familial allergy in our con-

*Mull-soy (powdered), The Borden Co.

trol groups was 100 per cent, and the incidence of allergy in our infants about 60 per cent. One would certainly expect a higher incidence of allergy in monozygotic twins, but if twinning has nothing to do with the incidence of allergy in the twins as Bowen's work so definitely proves, if Bowen's family histories were 100 per cent positive, then the incidence in his twins would have been 60 per cent, exactly as we found. One difference between our work and Bowen's, however, may possibly be that the great majority of our cases were followed from birth, some up to 10 years or longer, whereas Bowen's cases were studied at whatever age they happened to come under his observation. Under such circumstances certain undeniably allergic diseases could easily have been overlooked.[4] We are also glad that Bowen agrees with us as to the feeding of breast milk. If the mother of a potentially allergic infant cannot or will not nurse, however, we urge the use of soybean milk or another substitute milk based on similar principles as an alternative feeding rather than cow's milk.

We submit that the most important factor in any kind of investigation is the application of good common sense. It is important to remember that statistical techniques should be the servant and not the master of the scientist. One could well imagine what would have happened if Jenner, for example, in his work on the prophylaxis of smallpox, had applied the principles of investigation so strongly advocated by our critics. Yet, in planning in advance such a work as Jenner's, it would theoretically be an ideal situation for the application of such principles.

In the course of our experiments we recognized the problems involved and discussed them at length with our statistician. To the best of our ability, we did not allow prejudices to influence us in the selection of the nonrelated control group. We do not honestly feel that the chance prejudices were enough to be misleading. The final judgment of the wisdom of this conclusion will come perhaps only when the weight of each bit of evidence such as we presented is checked by others (each bit being subject to the same criticism) is overwhelmingly in favor or in contradiction to our published conclusions.

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SARCOIDOSIS: A HYPERSENSITIVITY DISEASE

Discussion of Three Cases

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DESPITE the fact that sarcoidosis has attracted much attention during the past few decades, little is known about its etiology, dissemination, or relationship to other forms of granuloma. The systemic manifestations of sarcoidosis were first emphasized by Schaumann[1] in 1914. He concluded that it was a special form of infectious granuloma, having no relation to tuberculosis. Since the course was relatively a benign one, he suggested the term "lymphogranulomatosis benign" as contrasted with "malignant lymphogranulomatosis" or Hodgkin's disease. Although leishmaniasis,[2] syphilis,[3] leprosy,[4] silica,[5] trauma,[6] and beryllium[7] have all been reported as etiologic agents, the coexistence of sarcoidosis, periarteritis, and panarteritis[8-11] suggests that its pathogenesis may be the same as various collagen diseases. Jackson and Kass[12] in a previous paper discussed the relationship between periarteritis nodosa and sarcoidosis. The clinical response of sarcoidosis to cortisone therapy[13] suggests that its protean manifestations may be those of a hypersensitivity disease whose prognosis may be governed by the intensity and pathogenicity of the etiologic agent.

The following three cases are presented to illustrate evidence suggesting that sarcoidosis and sarcoid lesions belong in the group of hypersensitivity diseases and reactions, respectively.

Case 1.—The patient, D. N.,† is a 29-year-old World War II veteran who was first hospitalized at this facility in 1946 with the clinical findings of erythema nodosum which were associated with a rather marked hilar adenopathy. A diagnosis of rheumatic fever was made. In 1951, he was readmitted to the medical service with a history of tiredness, thirty-pound weight loss and a marked generalized lymphadenopathy was noted. A roentgenogram of the chest, taken on admission, revealed no hilar adenopathy but a shaggy linear and granular infiltration was observed throughout both lung fields. This was heaviest in the lower lung fields, where it became partially confluent. The first strength PPD was negative. There was no reversal of the A/G ratio. The only significant physical findings were a hepatosplenomegaly and a marked enlargement of the cervical, axillary, epitrochlear, and inguinal glands. A biopsy of the left axillary node was performed and the diagnosis of sarcoidosis was made. Oral cortisone therapy was started; the patient was given 200 mg. per day for two days and 100 mg. per day for twenty days. A repeat node biopsy was done on the seventeenth day of cortisone therapy. The granulomatous lesions were decreased in number and a collagenlike precipitate appeared both within and bounding the noncaseating tubercle. A comparative chest roentgenogram, taken at the time of the second biopsy, showed some infiltrative changes at both bases which appeared reduced in prominence and extent. Similar studies performed six weeks after the cessation of the hormonal therapy revealed

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†This case has been presented elsewhere in greater detail.[14]

a mild regression of the lesion. About one year after discharge from the hospital, his condition deteriorated, necessitating rehospitalization. Cortisone therapy was reinstituted and a marked improvement in his clinical condition was again noted. It is hoped that a sustained remission can be induced by a prolonged course of hormonal therapy.

Summary.—The first manifestations in this case were those of erythema nodosum and hilar adenopathy. Five years later the patient returned with protean manifestations and a microscopic diagnosis of sarcoidosis was made following a lymph node biopsy. A course of cortisone therapy was followed by a marked subjective and objective improvement.

CASE 2.—D. D. was a 35-year-old white male who was admitted to the medical service with the chief complaint of bilateral swelling of the knees and ankles, duration two days. This was preceded by a feeling of malaise for one week. The past history revealed the following illnesses: dementia praecox, 1944; bilateral internasal antrotomy, 1945; bronchopneumonia, 1949; and otitis and sinusitis, 1951. Following the ingestion of milk and milk products he developed a generalized urticaria. He had an allergic rhinitis and there was a marked sensitivity to dust. Physical examination revealed an obese, white male in no acute distress. Blood pressure was 120/84 mm. Hg. There were no significant cardiovascular or pulmonary findings. The liver and spleen were not palpable. There was some atrophy of the right testicle. The knee and ankle joints were both tender, warm, and slightly swollen. No redness was noted, but there was some limitation of joint motion.

Serologic examination for syphilis was negative. White blood count was 7,100. The differential showed 61 per cent neutrophils, 30 per cent lymphocytes, 2 per cent monocytes, and 7 per cent eosinophils. Sedimentation rate was 35. The blood chemistries were reported in milligrams per cent as follows: N.P.N., 38.3; creatinine, 1.5; glucose, 97; cholesterol, 245; phosphorus, 4.5; and calcium, 5 meq. per liter. Total protein was 6.1 Gm. per 100 c.c.; albumin, 4.1; globulin, 2.0 with an A/G ratio of 2. The urinalysis was within normal limits. No acid-fast bacilli were found in the sputum and the skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis were negative. The roentgenographic and fluoroscopic examination of the chest showed the cardiac shadow to be within normal limits. The trachea was in the midline. The hilar shadows were increased, and the superior mediastinum appeared widened by a well-defined, homogenous density (Fig. 1, *A*). A barium swallow showed that neither the trachea nor the esophagus was displaced by the mass. Roentgenograms of the hands showed the normal bony density, and the articulating surfaces were smooth and regular.

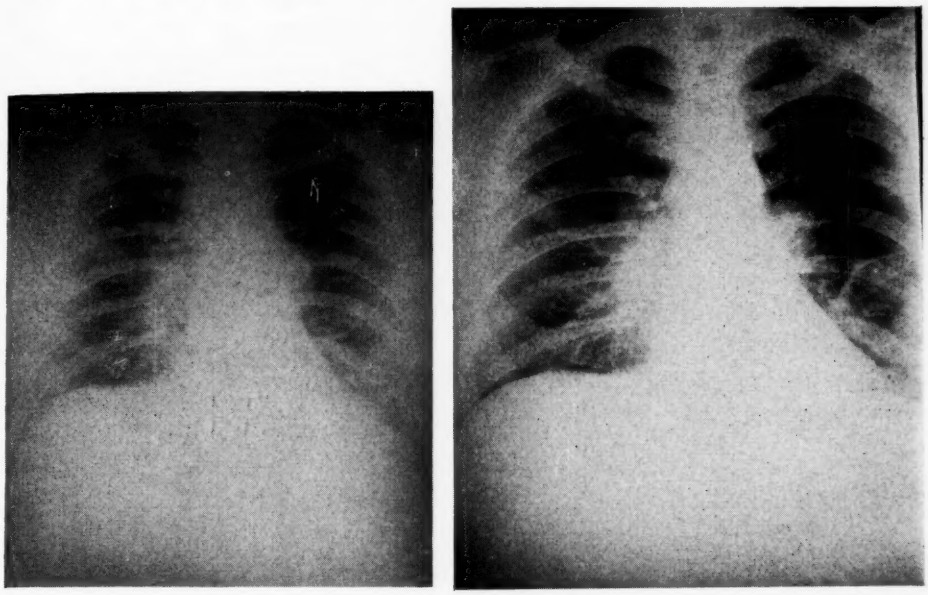
Although sarcoidosis was suspected, the diagnostic difficulties were accentuated by the lack of both Kveim's antigen and an accessible lymph node. Bronchoscopy was negative. The roentgenographic findings, however, indicated that a supraclavicular node biopsy might be helpful. Under local anesthesia a supraclavicular node was removed and the microscopic examination showed the tissue to be composed of miliary and conglomerate granulomatous lesions consisting of irregularly proliferating epithelioid cells and numerous multinucleated giant cells. The giant cells were often centrally placed and surrounded by the proliferating epithelioid cells. A few lymphocytes, scattered throughout the granulomatous areas, were present. A diagnosis of Boeck's sarcoid was made (Fig. 2, *A*). Tissue stains for tubercle bacilli were negative.

Examination of the nasopharynx revealed a purulent drainage from the mucosa around the left eustachian orifice. The nasal mucosa appeared reddened. Some mucopurulent material was aspirated from each antrum. The right eardrum was severely contracted with a diffuse injection along the handle as well as the periphery of the eardrum. A diagnosis of acute nasopharyngitis, right acute catarrhal otitis media, and chronic allergic rhinitis was made.

The patient was placed on 25 mg. of cortisone four times a day for 14 days. The joint swelling disappeared within a few days and a marked sense of well-being was noted. Roentgenograms taken following the conclusion of cortisone therapy showed a regression in the hilar adenopathy (Fig. 1, *B*). Another supraclavicular lymph node biopsy was performed and six small nodes were removed. Sections of the biopsy differed from the previous one. The granulomatous lesions were much smaller and a larger amount of collagen-like precipitate

appeared in the stroma between the tubercle-like lesions. The giant cells were not as prominent (Fig. 2, *B*). The repeat sedimentation rate was normal.

Summary.—A diagnosis of Boeck's sarcoid was made in a patient with a known history of sensitivity to dust and milk products. A marked subjective and objective improvement was noted following the institution of cortisone therapy. The presence of joint symptoms may or may not be a manifestation of sarcoidosis.[15, 16]



A. *B.*

Fig. 1.—*A*, Roentgenogram of the chest prior to cortisone therapy. *B*, Comparative chest roentgenogram following therapy showed a regression in the size of the hilar adenopathy.

CASE 3.—This patient, F. B., a 57-year-old white male, was readmitted to the E.N.T. Service* on April 7, 1952, following an outpatient examination which showed him to have a metastatic carcinoma involving the lymphatics of the right neck. He had originally been admitted on April 20, 1951, with the presenting complaint of hoarseness of six months' duration. At that time he was found to have a large subglottic squamous cell carcinoma. Initially he refused surgical intervention but consented to same because of complications following roentgenographic therapy. On July 4, 1951, a laryngectomy and a total, wide-field operation was performed. No significant nodes were palpated in the carotid sheath during the operation. On March 18, 1952, the entire right cervical chain from the jugulo-digastric to the jugulo-omohyoid nodes were found to be enlarged. They were firm, movable, and nontender. Physical examination showed a well-developed, well-nourishd, totally aphonic white male with a readily understandable esophageal voice. Indirect laryngoscopy showed no evidence of a tumor recurrence within the hypopharynx. Blood pressure was 164/100 mm. Hg in both arms, and the pulse was 84, full and regular. There was a marked increase in the AP diameter of the chest. No hepatosplenomegaly was noted. Aside from the cervical chain nodes there was no generalized lymphadenopathy.

The routine admission laboratory work including a chest x-ray was entirely within normal limits.

On April 11, 1952, under combined local and general anesthesia, the patient underwent a right radical neck dissection. Pathologic examination of the removed material showed

*We are grateful to Dr. Harry Knauff, Chief, Ear, Nose, and Throat Service, for the privilege of seeing this patient.

nodes in the jugulo-digastric area to be invaded by a metastatic carcinoma (Fig. 3*A*). The tumor tissue showed large sheets and cords of anaplastic squamous cells. Impression was a metastatic squamous cell carcinoma involving lymph nodes and soft tissue, also a hyperplastic lymphadenitis.

Tissue which had the appearance of necrotic and fibrotic fat was also removed from the supraclavicular area (Fig. 3*B*). Section revealed many granulomatous foci, which showed no areas of central necrosis. The granulomatous foci consisted mainly of epithelioid cells in association with a few scattered lymphocytes. An infrequent giant cell of the Langhans type was seen. The impression was a sarcoid lesion.

Fig. 2*A*.—Section of a supraclavicular node, prior to cortisone therapy, demonstrates an almost conglomerate granulomatous lesion.

A course of roentgen therapy consisting of 13,600 r followed the surgery. He was first seen by one of us (I. K.) on April 28, 1953, at which time a careful search was made for evidence of an existing generalized sarcoidosis. There was no cutaneous or uveoparotid involvement. The total protein was 7.6, albumin 4.3, and globulin 3.3 with an A/G ratio of 1.3. Intermediate strength PPD was reported as two-plus. Roentgenograms of both the hands and feet showed no sarcoid involvement. White count was 8,100, 62 per cent neutrophils, and 38 per cent lymphocytes. Red blood count 4,210,000 with 84 per cent hemoglobin. Total cholesterol 214 with 63 per cent esters. Cephalin flocculation 1+ in 48 hours, thymol turbidity 2 units, alkaline phosphatase 4.9 Bodansky units, and serum bilirubin 0.2 mg. per cent.

Bromsulfalein retention, 5 mg. per kilogram, showed no dye retention after 45 minutes. Following the cessation of roentgenographic therapy the patient was discharged from the hospital. He has been followed periodically with no significant change noted in his condition.

Summary.—This case was first seen by us because sarcoid changes were observed in the tissue removed in a radical neck dissection for nodes secondary to a squamous cell carcinoma of the larynx. No evidence of sarcoidosis per se was found. No treatment was felt to be indicated for the sarcoid lesion since the latter tissue was thought to have been completely removed.

Fig. 2*B*.—Following therapy a marked reduction in the tubercle-like lesions was noted. Histologic changes such as these have been observed in the spontaneous healing of a sarcoid lesion.

DISCUSSION

There appears to be considerable justification for including sarcoidosis under the classification of hypersensitivity diseases.[8-11] A similarity between the lesions of sarcoidosis and that of a beryllium granuloma, an accepted hypersensitivity reaction, has been described.[17] Although 25 per cent of the cases of sarcoidosis are associated with tuberculosis, it is felt that the association is a hypersensitivity reaction to the tuberculous toxin rather than to the tubercle

bacillus per se. Of the three cases presented, two patients displayed symptoms of a hypersensitivity reaction prior to the onset of sarcoidosis. In the first case, the earliest hypersensitivity symptoms noted were those of erythema nodosum and hilar adenopathy, and the second case showed a marked antecedent sensitivity to dust, milk, and milk products. This should not imply that sarcoidosis occurs only in people with allergic backgrounds. Rather the nature of the morphologic reaction in response to a plurality of stimuli, including malignancy, is such that it seems entirely possible that the proper antigen or antigens in a sensitized or predisposed person may produce erythema nodosum or food allergies on one occasion and the protean manifestations of sarcoidosis on another.

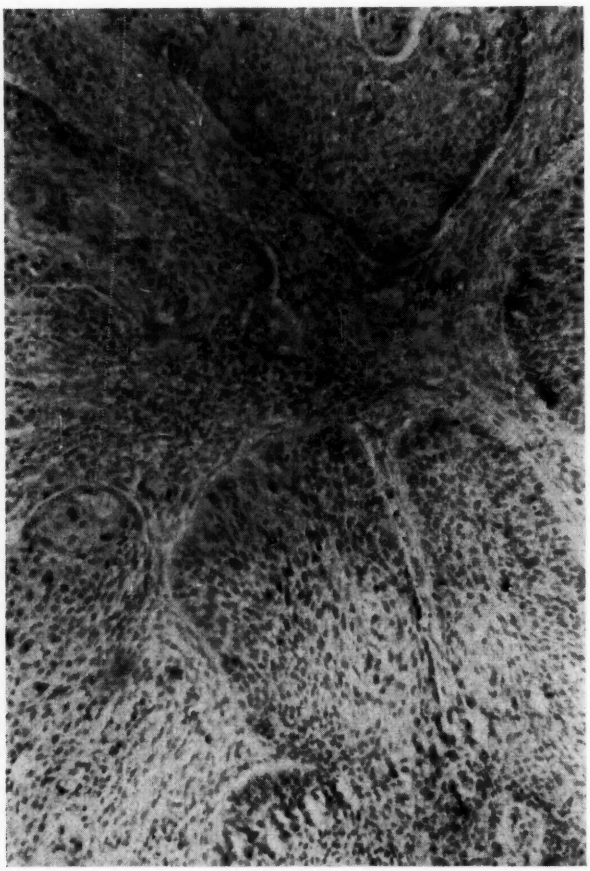


Fig. 3A.—Low-power section of the metastatic squamous cell carcinoma.

There may be some objection to defining erythema nodosum as a hypersensitivity reaction, since voluminous reviews of the literature have associated erythema nodosum with such diseases as tuberculosis, rheumatic fever, coccidioidomycosis, lymphogranuloma inguinale, and leprosy. It has also been described as an accompaniment of sensitivity to a variety of drugs such as bromides,

iodides, and sulfonamides. Favour and Sosman,[18] in a review of 155 patients, 61 of whom were followed for one to twenty years, concluded that erythema nodosum was a hypersensitivity disease with a plurality of causes. As to the coexistence of erythema nodosum and hilar adenopathy, the same authors found this to be present in 13 per cent of the cases. It was their belief, as well as that of others, that although the possibilities of tuberculosis, coccidioidomycosis and sarcoidosis should be considered, the hilar enlargement may simply be a part of erythema nodosum of nonspecific etiology.

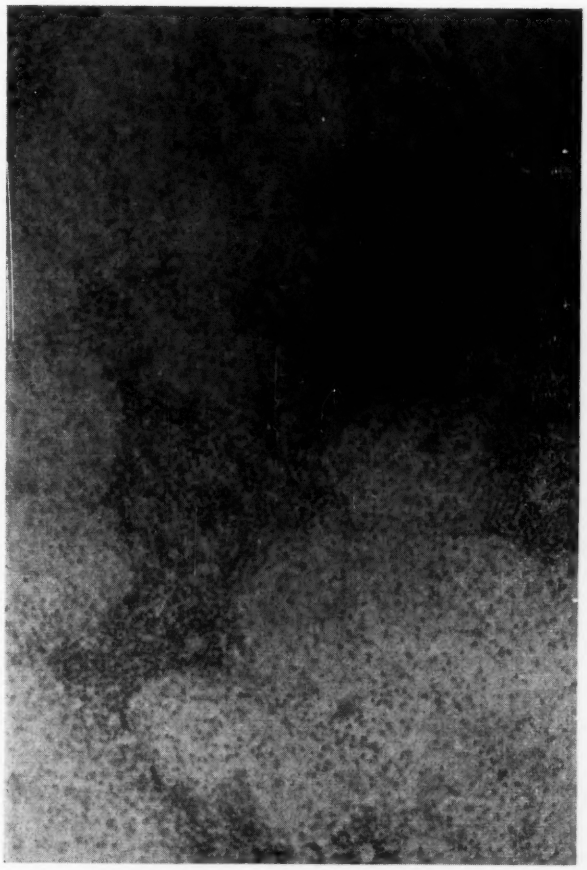


Fig. 3*B*.—Section of the localized sarcoid granuloma associated with the carcinoma.

The third case differs, however, from the other cases inasmuch as the involvement appears to be a localized one. Gherardi[19] first reported a case of carcinoma of the bile ducts associated with what he described as Boeck's sarcoid in the regional lymph nodes. Since then others have noted that neoplasia and granulomatous inflammation may coexist in one site or in one region of the body.[9, 36] Although the coexistence may be fortuitous, the presence of the sarcoid lesion in the tissue drained by the affected lymphoid tissue may indicate

a hypersensitivity reaction, resulting from the presence in the tissues of irritant products of a lipoidal or lipoprotein nature, such as stearin and palmitin.[35] Because this is only a localized tissue response, the term sarcoid lesion is used as opposed to sarcoidosis, which indicates a systemic disease entity.

A rather similar response is noted in the three cases of histoplasmosis with disseminated sarcoid lesions reported by Iverson.[20] This is explained as a reaction to the fungi, which upon entering the blood stream are carried to the lymph nodes where, because of better tissue-immunity, the fungi may be rapidly killed, setting free antigen in circulation with resulting production of sarcoid lesions. Teilum called the immunologic response an allergic hyperglobulinosis.[22]

In the third case it would have been interesting to determine the response of the sarcoid lesion to cortisone therapy once the carcinoma had been removed. The surgeon, however, felt that the involved tissue had been completely removed and that a repeat biopsy following hormonal therapy would be unrevealing.

In a previous paper, clinical and histologic evidence was presented to show the relationship between sarcoidosis and periarteritis nodosa, the latter being an accepted hypersensitivity disease.[12] The same clinical phenomena noted by Baggenstoss and associates[23] in periarteritis nodosa following hormonal therapy has been observed in sarcoidosis. The patients experienced a prompt subjective relief, a subsidence of the fever within 24 to 72 hours, and the gradual decrease of an elevated sedimentation rate to normal. In both diseases a partial relapse occurred after the administration of cortisone was discontinued and an improvement following the resumption of hormonal therapy was noted.

Likewise the clinical pictures in periarteritis nodosa and sarcoidosis present certain similarities such as weakness, loss of weight, fever, dyspnea, cough, hematuria, and albuminuria. A generalized lymphadenopathy was frequently found in both illnesses and pulmonary involvement occurred in 40 per cent of the cases of periarteritis nodosa.[24] Histologically the response in both diseases to cortisone was similar. The inflammatory reaction tended to become fibrotic under treatment. Sometimes in the hormonal treatment of periarteritis nodosa, Baggenstoss noted that the fibrotic process of healing resulted in the obliteration of the lumina of vessels. This caused infarcts which were particularly numerous in the kidney, heart, and intestinal tract. In some cases of sarcoidosis, a failure in improvement of pulmonary function has been attributed to the development of a severe fibrosis.

McClement and associates[25] have recently defined the types of pulmonary sarcoidosis and they feel that the case in which the least physiologic improvement in pulmonary function should be expected is the one in which there appears to be an extensive sarcoid involvement of the alveolar-capillary septum. The fibrosis associated with healing following cortisone therapy causes a change in lung volume and a disturbance in alveolar-capillary gas exchange consistent with chronic pulmonary emphysema. Our cases experienced no subjective change in pulmonary function following treatment.

The response of sarcoidosis to corticotropins and cortisone, like other hypersensitivity diseases, tends to be a variable one which is conditioned by

many factors. Thus it was not surprising that Thorn[26] first reported that ACTH was not effective in the treatment of sarcoidosis. Miller and Bass,[27] however, later effectively treated a case of pulmonary and glandular sarcoidosis with ACTHAR-C. Sones and associates[28] were the first to treat sarcoidosis with cortisone, and they noted a marked improvement in the widespread and severe pulmonary, cutaneous, lacrimal, parotid, and lymph node lesions. Shrinkage of peripheral and mediastinal nodes usually occurred within 6 to 10 days after cortisone therapy was started. Fresh lesions appeared to give the best results.

Obviously, the problem of determining the site and mode of cortisone's action as well as accounting for its varying effectiveness in hypersensitivity reactions awaits further clarification. As more cases are reported, however, it becomes increasingly apparent that the connective tissue is not stable but exists in a labile state which is under the control of the opposing hormonal forces. It is believed that the hypersensitivity agent (whatever it may be) causes, in susceptible persons, an antigen-antibody reaction with increase in the gamma-globulin, eosinophils, plasma cells, and lymphocytes. If the noxious stimulus lasts long enough and is strong enough, as in allergic states, there will be a hormonal imbalance with the proliferation of the connective tissue and granuloma formation. Recently Simpson and associates demonstrated a corticosteroid capable of such physiologic activity in a mammalian's cortical extract and adrenal venous blood.[37]

Selye[29-33] feels that the organism attempts to re-establish homeostasis by increased gluco-corticoid (ACTH) production. The gluco-corticoid desensitizes the involved tissue and results in a decrease of the eosinophils, plasma cells, lymphocytes, antibody formation, and suppression of membrane permeability. Hench[34] feels that "cortisone may correct a relative, not an absolute, deficiency and satisfy an increased tissue request for the hormone."

If we remember the analogy of other hormones, it may be years before the site and mode of cortisone's action are decided. The paradox currently confronting the clinician is whether masking the symptoms with cortisone permits the illness to manifest itself in some other way. The diabetic, because of insulin, no longer dies in coma, but lives to develop renal and arterial lesions. Only continued study will reveal if the sequela sometimes associated with the use of cortisone in sarcoidosis, periarteritis nodosa, is a lesser evil than the disease itself.

SUMMARY

Evidence has been presented suggesting that sarcoidosis and sarcoid lesions belong in the group of hypersensitivity diseases, and reactions, respectively.

1. Sarcoidosis and hypersensitivity diseases display a similar morphologic reaction to stress.

2. Two of the three patients presented displayed symptoms of a hypersensitivity reaction prior to the onset of sarcoidosis.

3. A sarcoid lesion was observed in the third case. This was thought to be a localized hypersensitivity reaction, secondary to the irritant products of a

coexisting malignancy. The term "sarcoid lesion" is used to define a localized granulomatous reaction to a wide variety of injurious agents, whereas sarcoidosis indicates a systemic disease entity.

4. The initial clinical similarities as well as the response to hormonal therapy suggest the inclusion of sarcoidosis as a hypersensitivity disease.

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THE ALLERGIC EPIGASTRIC SYNDROME

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THE allergic epigastric syndrome is characterized by epigastric pressure, fullness, burning, soreness, xiphoid tenderness, aching, and pain in varying degrees; the pressure, fullness, and/or burning are present in practically all cases. This syndrome has not been reported in previous articles.[1] Nausea, vomiting, belching, and sour stomach occur less frequently. Burning, pressure, and/or aching may also occur under the sternum or the neck, throat, shoulders, or arms, suggesting cardiac angina, peripheral neuritis, or arthritis. Occasionally severe buccal and/or pharyngeal burning with erythema and even diffuse papular or white patchy eruptions of the mucosa and aphthous stomatitis may be present. Globus hystericus may occur and be allergic in origin. Soreness, pain, or cramping in the rest of the abdomen is not infrequent. Constipation or diarrhea, with or without mucus, may be a problem. Headaches, at times severe and migrainous, may be present. Fatigue, exhaustion, dullness, drowsiness, confusion, irritability, generalized aching, and other symptoms of allergic toxemia and fatigue[2] occur with varying frequency. Manifestations from allergic reactivity in other body tissues may exist although the gastric and other adjacent tissues may be the only shock areas of allergy. Symptoms usually have lasted for long periods, in the present series from one-half to fifty years, with an average of thirteen years. Although usually persistent with irregular variations, they may be intermittent with nearly or complete intervening relief.

Physical examination, laboratory studies, and x-rays of the upper gastrointestinal tract, colon, and gall bladder usually are negative. In this series an apparently inactive or slight duodenal ulcer was present in two cases, in one case pyloric spasm[7] and irregular segmentation of the small bowel occurred, and apparent hypertrophy of the rugae was present in one case. In one case gallstones were present, but cholecystectomy did not relieve symptoms until the proper elimination diet was used. Because of the great frequency of negative physical and laboratory findings, psychoneurosis or nervous indigestion had been assumed in many cases. This should not be assumed unless allergy especially to foods has been considered with adequate and experienced study.

DIAGNOSIS AND TREATMENT

When the patient's history reveals any of the epigastric symptoms, with or without others outlined above, this allergic epigastric syndrome should be suspected. The diet history may reveal disagreements for foods present in 56 per cent of these cases or less frequently dislikes for foods, especially for milk. These disagreements and dislikes are suggestive of possible food allergy but are not necessarily diagnostic. Exaggeration of symptoms in the fall,

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winter, and spring occasionally has occurred,[3] thus suggesting food allergy. In one case symptoms were greatly exaggerated during the pollen seasons. Large pollen reactions and relief with pollen desensitization indicated gastrointestinal pollen allergy. Other manifestations and a family history of allergy are not necessarily present.

Skin testing by the scratch method is done with all important food and inhalant allergens. A few questionable or slightly positive reactions to foods in a few patients did not indicate any or all of the allergenic foods, indicating according to our experience the cumulative type of chronic food allergy rather than the immediate type which usually gives large scratch reactions. We do not perform intradermal tests with foods because of the many false and indefinite reactions which are obtained. Six patients gave positive reactions to pollens which were associated with pollen hay fever in three cases and gastrointestinal allergy in one case.

Because of the negative or fallible skin tests, diet trial has been used to study possible food allergy. For this the senior writer's fruit- and cereal-free elimination diet[4] has shown that fruits, spices, condiments, beverages, milk, chocolate, various vegetables, cereals, egg, and fish, in order of frequency and in various combinations were responsible in all of the patients in this reported group except for the pollen-sensitive patient. This diet is modified by eliminating foods to which definite dislikes or disagreements exist and by deleting foods which may cause abdominal distress, such as legumes. Then rice, to which there is infrequent gastrointestinal allergy, may be substituted for legumes, making rice-potato bakery products available. If the above diet does not give some or definite relief in ten to fourteen days, a minimal fruit-free elimination diet[5] should be tried before ruling out food allergy as the cause. This contains rice, white potato, tapioca, cooked with sugar and flavored with burnt sugar or caramel, lamb, chicken, carrots, peas, and/or squash, sugar, salt, and water in amounts containing 60 to 80 Gm. of protein and 1,500 to 2,200 calories. Vitamin C is given unless rare allergy to it occurs. Other synthetic vitamins are ordered as indicated. Strict adherence to the diet is required. Inhalation of odors of allergenic foods, especially fruits, may prevent relief. If improvement occurs in two weeks, the diet should be continued until symptoms are practically or completely absent. A slight error may reproduce symptoms for three to seven days. In three to six weeks other vegetables, cereals, egg, and milk may be added, one daily for four to five days, eliminating any which reproduce symptoms. Since fruits, uncooked vegetables, flavors, and condiments are frequent causes, they should be added last. An additional discussion of this important diet trial will be found in other communications of the writers.

DRUGS

Since the elimination of all allergenic foods controls this epigastric syndrome and associated symptoms, diet manipulation should be continued toward this goal. Unless this is accomplished, aspirin and at times codeine may be justifiable. Antispasmodics and sedatives are rarely beneficial. Although

small doses of cortisone increase tolerance for foods and control mild residual symptoms in some patients, it is infrequently necessary or justified because of the excellent relief resulting from the adequate and proper use of the elimination diets.

COMMENT

Epigastric symptoms relieved by elimination diets are best explained by gastric allergy and allergic reactivity in the peritoneum and other local tissues. It is possible that even the pancreas may be involved. The fullness and pressure present in every case may be due to localized edema and possibly to disturbed peristalsis. Burning, present in many cases, suggests gastric erythema and edema similar to that seen in the oral mucosa when burning in the throat and mouth occurs, either alone or in association with the epigastric syndrome. Gastroscopy in two patients has revealed moderate erythema and edema and in one patient apparently enlarged rugae. This examination was refused or not advised a second time and in most patients initially, largely because of the rapid improvement and relief with the elimination diet, the expense, and the associated discomfort from the examination.

Roentgen-ray studies of the upper gastrointestinal tract were negative in 32 patients. Hypertrophied-appearing rugae were seen in one woman who had extremely severe symptoms. These findings disappeared after a few months of excellent relief with the proper elimination diet. Pyloric spasm and an irregularly segmented small bowel, which could have been due to food allergy, occurred in one patient. Previous x-rays of the upper gastrointestinal tract had been negative in 13 patients. Slight or inactive duodenal ulcer was seen in two patients in whom the epigastric and other symptoms were dominant and relieved by the elimination diet. Symptoms previously attributed to a duodenal diverticulum and psychoneurosis in one patient were relieved by elimination of his determined allergenic foods.

Food allergy has been a previously reported cause of gastrointestinal symptoms associated with gastric retention, pyloric and duodenal spasm and edema, and disturbed gastric and intestinal motility, as reported by Rowe,[7] Fries,[8] and Cooke.[9] Only four of our patients with this allergic epigastric syndrome, however, had such findings. Many of these patients had had one or more negative x-ray studies of the entire gastrointestinal tract and gall bladder and negative physical and laboratory examinations, with a usual conclusion of psychoneurosis, before obtaining relief with our elimination diets. Thus it is probable that the food allergy producing these symptoms usually fails to produce changes demonstrable by x-ray. Although patients with duodenal ulcer confirmed by x-ray are not included, frequent relief of their symptoms with the elimination diets utilized in the control of this allergic epigastric syndrome indicates possible food allergy as one cause of duodenal ulcer. We are continuing the study of such possible duodenal allergy.

Substernal pressure, aching, and burning may also be associated with or may be worse than the epigastric symptoms. Erythema and edema of the esophagus and allergy in the adjacent mediastinal tissues is a probable ex-

planation. Aching and at times burning may extend into the lateral chest, the sides of the neck, shoulders, and rarely into the arms, suggesting cardiac angina with resultant unnecessary restriction in physical, occupational, and social activities before the symptoms are relieved by elimination diets. Recently a gardener was relieved of such symptoms in two weeks with a minimal fruit-free elimination diet, having avoided all physical work for three years, being able to resume such work without any former symptoms.

The constipation and/or diarrhea occurring in these patients may also be relieved by elimination diets, again indicating food allergy as the probable cause. Failure to relieve constipation, especially of long standing, does not rule out allergy to foods and possibly to other allergens since longer use and manipulation of the elimination diets or control of other allergies might be required to obtain such relief. As yet practically no studies of constipation from the allergic viewpoint have ever been made. That the colon is frequently subject to allergy is indicated by our studies and successful treatment of many cases of chronic ulcerative colitis,[6] allergic diarrhea, mucous colitis, the unstable or irritable colon, allergic proctitis, and pruritus ani.

Most of the headaches[1] in these patients were associated with nausea and vomiting and were relieved with the diet which also controlled the epigastric syndrome and associated symptoms. This indicated cerebral allergy as the probable cause. The usual relief of fatigue, confusion, nervousness, tension, and other symptoms of allergic toxemia[2] with the elimination diet has been especially gratifying to the patients.

CASE REPORTS

CASE 1.—A man of 51 years had had burning and pressure in the epigastrium, at times associated with sour stomach, for fifteen years for one to three hours after meals every two to three days and at times constantly from two to five days or longer. Recently this burning and sour regurgitation had been so severe that he had been in bed for four weeks. Similar prolonged attacks had occurred in 1944 and 1951 and at other times for one to two weeks. Treatment for duodenal ulcer in 1944 with a milk diet caused extreme constipation.

For twenty years he had had severe nuchal headaches lasting for twelve to twenty-four hours. These had decreased in frequency in the last year. No other symptoms had occurred.

Diet history revealed that milk, fruits, and tomato caused sour stomach. Onions, garlic, and condiments had caused distention.

Drug history revealed that morphine had caused dermatitis and Empirin and codeine had caused vomiting.

Family history revealed that his father had had severe abdominal pain with associated nausea for many years, relieved by the elimination of allergenic foods.

Blood count, urinalysis, sedimentation rate, and Kline test were negative. Skin tests by the scratch method gave no reactions to inhalants or foods.

With a minimal fruit-free elimination diet, epigastric burning ceased in seven days. Other foods were gradually added. Beets, sweet potatoes, celery, fruits, and milk have reproduced the symptoms.

CASE 2.—A woman of 49 years had had tightness and "knotting like a charleyhorse" in the epigastrium for at least twenty-five years after various foods, often associated with urgency, soft stools, gas, and lower abdominal cramping after meals. With this distress she had had severe back pain during the night, relieved by walking. These symptoms had been especially severe for four months. X-ray had showed apparent hypertrophic rugae. Gastroscopy, showed moderate edema of the mucosa.

For twenty years, aching of all joints had occurred. She wore a neck cast for six weeks six years ago. Since then recurrent pains with some swellings had continued, but she was better in hot weather. Fatigue and enervation, especially on awakening, had been present. Depression, frustration, and irritability had varied, largely due to lack of relief and "inability to do things." Symptoms had been attributed to nervousness. No other manifestations of allergy or other disease had occurred.

Diet history revealed that beef, cola drinks, possibly rye, and condiments had caused epigastric distress. Wheat and possibly egg seemed to cause aching in the joints.

There were no drug allergies.

Family history revealed that her father had severe egg allergy.

Cholecystectomy had been performed fifteen years ago and hysterectomy eleven years ago.

Physical examination, blood count, urinalysis, Kline test, sedimentation rate, and serum proteins were normal. X-ray of the gastrointestinal tract showed apparent hypertrophy of the rugae. Skin testing gave no reactions to foods or inhalants.

To study food allergy she was given the senior writer's fruit- and cereal-free elimination diet plus rice, Crisco, cottonseed oil, and vitamin C, 100 mg. daily, minus soya. In two weeks all symptoms were relieved. Since then, beef, milk, butter and oats have caused diarrhea and epigastric distress. Wheat caused aching in the joints. Several fruits, asparagus, and celery have caused epigastric symptoms. With the original diet her symptoms are controlled. It takes three to five days to recover from the allergenic foods. In three months after relief, x-ray revealed a normal stomach. Gastroscopy was refused.

CASE 3.—A woman of 61 years had had epigastric tightness, fullness, and a "lump in her stomach" for over six years, at first for one to two days every one to two weeks and then occurring every day for two to three months, causing "knots" in the upper abdomen. She had had a "delicate stomach" all of her life, "catarrh of the stomach" in babyhood, and vomiting attacks in childhood. Appetite had always been poor, and she had a feeling of fullness after small amounts of food. She had had slight constipation.

For six years perennial postnasal discharge, causing a hacking cough and at times gagging, had occurred.

Fatigue, confusion, forgetfulness, tension, restless sleep, and depression had increased in the last twenty years.

Diet history revealed no known dislikes or disagreements for foods. Drug history revealed that quinine had caused hives. Environmental history indicated no inhalant allergy. Family history indicated no predisposition to allergy.

Physical examination and laboratory tests were normal. Skin testing revealed 1- and 2-plus reactions to several animal emanations, miscellaneous inhalants, and pollens and to several foods. There was no correlation with the foods causing her clinical allergy except for 1-plus reactions to orange, pear, peach, and prune.

With the fruit- and cereal-free elimination diet plus rice, her epigastric distress, constipation, nasal allergy, fatigue, confusion, tension, and depression disappeared. Sleep was restful. She felt like working and "did things without effort," doing all her housework. Appetite was the best in her life and she no longer felt filled up with small meals.

The gradual addition of all foods after relief was assured has revealed allergy to milk and wheat, of which, at the end of one year, she can take small amounts every few days without symptoms. Spiced and seasoned foods are avoided. Fruits have not reproduced symptoms.

CASE 4.—A woman of 58 years had had "stomach trouble" since childhood, characterized by heaviness and burning in the epigastrium, much sour stomach, heartburn, belching, and regurgitation. For two years, burning of the mouth, lips, and tongue, with canker sores every two weeks, had increased. Since the age of six years she had had sick head-

ALLERGIC EPIGASTRIC SYNDROME
IN 50 PATIENTS

Age: 22 years to 64 years (Average 45 years)
Male: 20
Female: 30
Duration of Symptoms: ½ year to 50 years (Average 13 years)

	Percentage of Cases
Epigastric pressure or tightness	94
Epigastric distention	58
Epigastric burning	72
Substernal burning and aching	30
Precordial distress	14
Mid- and lower abdominal distress	18
Sour stomach	32
Heartburn	20
Belching	20
Cankers	22
Oral burning	6
Diarrhea	20
Constipation	40
Hemorrhoids	12
Pruritus ani	10
Headaches	38
Fatigue	42
Dullness and confusion	24
Nervousness	25
Depression	22
Nasal allergy	44
Bronchial allergy	14
Food disagreements	56
Food dislikes (usually milk)	18
Positive skin tests	
Foods	10
Pollens	18
Other inhalants	4
Family history positive for allergy	24

Stomach analysis:
- Normal: In 15 patients
- Achylia: In 2 patients

X-ray of upper gastrointestinal tract:
- Negative: In 32 patients
- Slight or inactive duodenal ulcer: In 2 patients
- Pyloric spasm and irregular segmentation of small bowel: In 1 patient
- Duodenal diverticulum: In 1 patient
- Hypertrophic rugae: In 1 patient
- Negative in previous studies: In 13 patients

X-ray of colon:
- Negative: In 25 patients
- Diverticulitis: In 2 patients

X-ray of gall bladder:
- Negative: In 24 patients

aches for one to two days every four to eight weeks. She had had hay fever in the spring for twelve years and moderate asthma during the pollen seasons for two years. Burning on urination had occurred from milk, coffee, and chocolate. Marked fatigue, restless sleep, and depression had been present for years.

Diet history revealed a lifelong dislike for milk. With the ingestion of the aforementioned foods, egg, and condiments, she had had gastric symptoms and headache.

Her drug and environmental histories were negative for allergy. Family history revealed that her mother and a brother had sick headaches.

Physical examination, blood count, urinalysis, Kline test, and gastric analysis were negative except for moderate hypertension. Skin testing showed 2- to 5-plus reactions to spring and tree pollens and slight reactions to several fall pollens. X-rays of the upper gastrointestinal tract and gall bladder were negative.

With the fruit-free elimination diet and vitamin C, her gastrointestinal and oral symptoms, headaches, fatigue, and restless sleep were relieved. With ingestion tests, fruits, condiments, egg, oats, and wheat have been the determined offenders. Pork produces diarrhea. The depression also is gone, relieved possibly by the diet or estrogens by mouth. She is "splendid and feels wonderful."

SUMMARY

The allergic epigastric syndrome is characterized especially by pressure, tightness, and burning in the epigastrium, associated with belching, heartburn, sour stomach, and mid- and lower abdominal distress in varying degrees and frequency.

Substernal burning, aching, and some soreness, at times precordial distress, erythema, and burning in the mouth and other results of oral allergy, headaches at times with nausea and vomiting, fatigue, mental confusion, and other symptoms of allergic toxemia, diarrhea, and especially constipation may occur in these patients.

Physical examination and laboratory studies were negative in all of the 50 patients in this series except for achylia in two patients. X-rays of the upper gastrointestinal tract were negative in 45 patients but revealed apparent hypertrophied rugae in one case and pyloric spasm with an irregularly segmented small bowel, best explained by food allergy, in another case. Although gastroscopy was refused or omitted in nearly all patients, largely because of the rapid improvement and later control by the proper diet, edema and erythema in one patient and probable hypertrophic gastritis in another patient were seen. Removal of gallstones in one case did not relieve the epigastric syndrome until the proper antiallergic diet was given. Symptoms relieved by the diets had been ascribed in several patients to nervousness, the attempted relief of which was ineffectual.

Food allergy was the evident cause of this syndrome and of the associated symptoms, except most of the constipation, in the 50 reported cases. This food allergy was indicated in some patients by a history of disagreements to foods and less often of dislikes for specific foods and rarely by clinically proved positive skin tests and in all cases by relief of symptoms by diet trial with the senior writer's indicated elimination diets.

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THE ACTION OF ACTH ON BLOOD HISTAMINE AND EOSINOPHIL LEUKOCYTES IN A CASE OF HERPES GESTATIONIS

FERDINANDO GIANOTTI, M.D.

FOLLOWING Kappeller-Adler's observations on the inhibitory activity of gonadotrophins on histaminase, and his findings of a marked decrease of this enzyme in toxemia of pregnancy related to the high levels of gonadotrophins, we have included the determination of histamine blood level in our researches in cases of herpes gestationis (H.G.).

We have previously observed in a case of herpes gestationis a histamine blood level of the order of 1,100μg per 100 ml. of whole blood. This value represents about 180 times the normal one, which is about 6 μg per 100 ml.

In the present paper we wish to report on the effect, obtained in the previously mentioned patient, on the histamine level and circulating eosinophils of the blood with the parenteral administration of ACTH.

METHODS

Determinations of the blood histamine level and of the number of circulating eosinophils have been performed repeatedly, before and four hours after the intramuscular injection of 25 mg. of ACTH (Armour). The same determinations were repeated successively before and after the administration of 100 mg. of cortisone intramuscularly.

Blood circulating eosinophils have been determined following the method of Thorn (normal value 100 to 140 eosinophilic cells per milliter).

The histamine blood level was estimated by the Code modification of the method of Barsoum and Gaddum (normal level about 6 μg per 100 ml.).

RESULTS

The results obtained in the patient with herpes gestationis and a high level of histamine in the blood are presented in Table I, and Fig. 1.

The findings observed contemporaneously in two control patients (a case of Duhring's dermatitis and another case of herpes gestationis with normal value of blood histamine, are presented in Table II.

DISCUSSION

From the aforementioned data is clearly evident the ability of ACTH to reduce, four hours after the administration to normal values very high initial levels of blood histamine, whereas physiologic initial levels remain quite unaffected.

From the Dermatologic Clinic, University of Milan, Italy (Director Professor A. Crosti).
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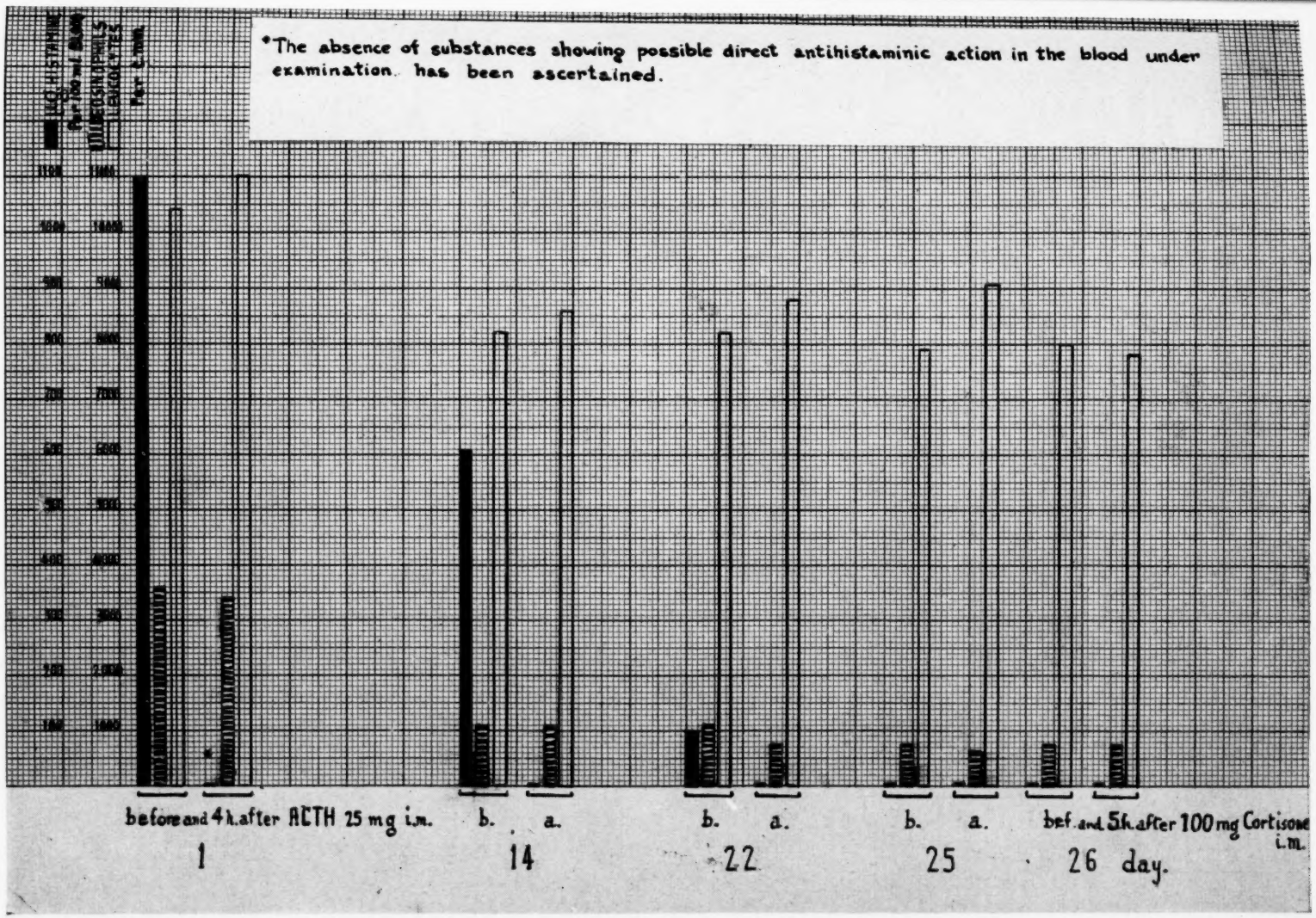
*The absence of substances showing possible direct antihistaminic action in the blood under examination has been ascertained.
before and 4 h. after ACTH 25 mg i.m.
b.
a.
b.
a.
b.
a.
bef. and 5h. after 100 mg Cortisone i.m.
1
14
22
25
26 day.

Fig. 1.

TABLE I

	BEFORE ACTH			FOUR HOURS AFTER ACTH 25 MG. INTRAMUSCULARLY		
	BLOOD HISTAMINE LEVEL (μg PER 100 ML.)	EOSINOPHILS (PER C.MM.)	LEUKOCYTES (PER C.MM.)	BLOOD HISTAMINE LEVEL (μg PER 100 ML.)	EOSINOPHILS (PER C.MM.)	LEUKOCYTES (PER C.MM.)
First determination	1,100	3,600	10,400	6*	3,400	11,000
Second determination (14 days later)	600	1,100	8,200	5	1,100	8,600
Third determination (8 days later)	100	1,060	8,200	5	770	8,800
Fourth determination (3 days later)	5	760	7,900	4	660	9,100
	BEFORE 100 MG. CORTISONE INTRAMUSCULARLY			FIVE HOURS LATER		
Fifth determination	6	750	8,000	6	740	7,800

*The absence of substances showing possible direct antihistaminic action in the blood under examination has been ascertained.

TABLE II

	BEFORE ACTH			FOUR HOURS AFTER ACTH 25 MG. INTRAMUSCULARLY		
CASE	BLOOD HISTAMINE LEVEL (μg PER 100 ML.)	EOSINOPHILS (PER C.MM.)	LEUKOCYTES (PER C.MM.)	BLOOD HISTAMINE LEVEL (μg PER 100 ML.)	EOSINOPHILS (PER C.MM.)	LEUKOCYTES (PER C.MM.)
Duhring's dermatitis	7	2,200	8,000	4	1,800	7,000
Herpes gestationis	4	1,100	7,000	3	580	8,000

It is interesting to note that the very high initial level of blood histamine observed in the first case of herpes gestationis, about 180 times the normal, represents, to our knowledge, the highest value so far reported for human beings with diseases of possibly allergic origin.

The behavior of eosinophils deserves some attention; they were decreased only exceptionally, also in case of high initial levels. This behavior has been observed in the first case of herpes gestationis with high blood histamine level as well as in the case of dermatitis herpetiformis (Duhring's dermatitis) with normal histamine level.

The number of leukocytes was not significantly altered, except for a slight tendency to rise after ACTH administration.

The effect of cortisone could not be definitely assessed because the histamine blood level had reverted to normal before its administration.

These observations suggest the following considerations:

1. The blood histamine level seems to be influenced by ACTH administration if it is higher than normal. The authors who studied this subject (Herbert, De Vries and Rose) have not observed this fact, probably because they have tested the effect of ACTH on subjects with normal histamine levels. It is noteworthy that Rose and co-workers demonstrated a great urinary excretion

of histamine in allergic patients treated with ACTH, soon after its administration, although they did not observe a significant modification of blood histamine levels.

2. The histamine blood level falls independently of the fall of circulating eosinophils; this is in accord with the previous observations of different authors (B. Rose, I; Herbert, De Vries and Rose). These authors consider that eosinophils are not histamine bearers.

3. The circulating eosinophils in the hyper-histaminemic patient are not lowered by ACTH administration; this would mean a state of adrenal insufficiency according to Thorn's test. In the acme of the disease the excretion of urinary 11-oxy-corticosteroids in the first case of herpes gestationis showed low results and similarly lower than normal was the result of the stimulation with 25 mg. of ACTH, the excretion changing from 0.250 to 0.400 mg. (method of Sprechler). (These findings will be reported elsewhere.) This was previously observed by us[4] in another case of herpes gestationis; on the contrary the good response of the urinary excretion of 11-oxy-corticosteroids in patients with Duhring's dermatitis is well known[1] also when the circulating eosinophils do not fall, above all in cases with high initial levels, as in our present control case.

The reported observations may be related to the researches of Rose and Browne[9] on animals, in which the histamine tissue levels were raised after adrenalectomy.

More recently, nevertheless, Dews, Code, and Higgins[3] did not find any difference in the histamine blood levels of normal and adrenalectomized rabbits before and after cortisone administration; they concluded that in these animals there was no interrelation between the adrenal and histamine blood level. This conclusion seems not acceptable in a general sense following these observations on our patient.

Acknowledgment is extended to Dr. Bonessa and Dr. Bocconi of the Hydrology Institute of Milan for determining the histamine blood levels recorded in this study.

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DIGITALIS ALLERGY WITH DEMONSTRABLE ANTIBODY

MILTON M. MOSKO,* AND ROBERT G. TAYLOR,** CHICAGO, ILL.

THIS is a report of a case of hypersensitivity to digitalis, manifested by urticaria, angioedema, and the formation of bullae in the skin, and in which was demonstrated direct specific immediate wheal-type skin reactions and passive transfer of specific reagins.

CASE REPORT

A 53-year-old Negro had noted dyspnea, fatigue, and swelling of his lower extremities for about three months when he consulted his family physician. Tincture of digitalis, 10 drops three times daily, had been prescribed, which he had taken from Nov. 8, 1952, until his admission to Hines Veterans Administration Hospital in January, 1953. There had been very little subjective relief during this treatment.

Physical examination at that time revealed bilateral crepitant râles at the bases of both lungs and mild edema of the feet. Treatment with rest, a low salt diet, and ammonium chloride provided excellent benefit, and on discharge he was asymptomatic.

On his return home, the patient again started taking tincture of digitalis. Twenty-four hours after initiating this medication, he noted urticaria of both arms, which progressed in another day to severe tense angioedema and numerous large bullae, so that he returned to the hospital presenting a brawny edema of both forearms covered with severe vesiculation of the skin. He was treated with cold soaks, Pyribenzamine, and ephedrine. No digitalis was given at this time. In five days the lesions had subsided markedly. On the sixth day he developed severe angioedema of the neck resembling a cellulitis, and during the next two days intermittent generalized urticaria. A history of using an ointment containing iodine was elicited, but a patch test with this substance was negative. By the tenth hospital day all skin lesions had completely disappeared.

On the fourteenth hospital day the patient showed some signs of frank cardiac insufficiency. The venous pressure was found to be 14 cm. of water, and the Decholin circulation time was 31 seconds. Accordingly, he was started on digitoxin by mouth. Four days later he developed urticaria and angioedema of the left upper extremity. After this had subsided he had intracutaneous tests on the right forearm with Decholin and digitoxin, with the latter giving a large immediate wheal reaction. Two days later the right forearm and arm became massively swollen and the skin covered with numerous large blebs. All medication was now stopped and in five days the swelling had completely disappeared.

Ten days later he again showed signs of myocardial failure and oral digitoxin therapy was started. Within three days he again developed severe swelling and vesiculation of the skin of his left arm. Digitoxin was stopped and the lesions gradually subsided. A few weeks later, direct skin testing was attempted with various digitalis preparations, and that night he developed a swelling on the back of his neck, plus edema of the left arm. A week later, after intracutaneous testing of the right forearm, he developed angioedema and bullae of the entire right arm. Two weeks later the left arm was used for additional intracutaneous tests with digitalis and in three days the entire left arm erupted severely with swelling and bullae. Since his discharge, at which time he was warned against the use of any digitalis preparations, he has remained free of urticaria, and has remained comfortable by restricting his activity and staying on a low salt diet.

Presented at the Tenth Annual Meeting of The American Academy of Allergy, Houston, Texas, Feb. 1-3, 1954.

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*From the Department of Medicine and the Allergy Unit, University of Illinois College of Medicine.

**From Hines Veterans Administration Hospital.

A review of the results of skin testing in this patient, summarized in Table I, showed positive immediate wheal reactions for digitoxin, lanatoside C, and Digilanid, questionable reactions to the whole digitalis leaf, and negative reactions for squill glycoside, ouabain, and strophanthin. Identical tests on three control subjects were all negative. Passive transfer was positive for digitoxin on two recipients with negative controls. Lanatoside C gave a positive passive transfer in one of two test subjects; but transfers for the whole leaf, ouabain, and strophanthin were negative.

Fluid aspirated from the bullae and used for passive transfer gave results similar to those of passive transfer with serum, positive reactions being elicited with digitoxin and lanatoside C, and negative reactions with squill and the whole leaf.

Serum from another patient thoroughly digitalized with whole leaf was used as a testing substance. The direct immediate skin reaction in our patient was positive, as was a passive transfer to a recipient, and controls in each test were negative.

TABLE I

	DIRECT		SERUM PASSIVE TRANSFER				BULLA PASS. TRANS.	
			TRANSFER #1		TRANSFER #2			
	PATIENT	CONTR.	P. T.	CONTR.	P. T.	CONTR.	P. T.	CONTR.
Digitalis leaf (Digilusin)	±	0	0	0	0	0	0	0
Digitoxin (Crystodigin)	+	0	+	0	+	0	+	0
Lanatoside C (Cedilanid)	+	0	+	0	0	0	+	0
Ouabain	0	0	0	0	0	0	0	0
Strophanthin	0	0	0	0	0	0		
Squill glycoside (Scillaren B)	0	0	0	0				
Lanatosides A, B&C (Digilanid)	+	0	+	0				
Serum of P. T. Digitalized with whole leaf	+	0	+	0				

DISCUSSION

Acquired sensitivity to digitalis must be rare because of the paucity of such reports. It was recognized early, however, for Morrow[1] in 1887 mentioned several cases, and quoted Behrand and Traube as having described others. In 1940 Cohen and Brodsky[2] reported a case of urticaria produced by tincture of digitalis in which the patch test was negative. Early in 1953 Wolfe and Geiger[3] also reported a case of urticaria produced by digitalis. They tried six different preparations, namely, digitalis whole leaf, digitoxin, Digoxin, Digilanid, lanatoside C, and squill glycoside and were able to reproduce the urticaria with all these drugs. They suggested that the allergic response could be attributed to the cyclopentenophenanthrene nucleus which is common to all of these cardiotonic glycosides, since these digitalis derivatives are actually from three different species, *Digitalis purpurea, Digitalis lanata,* and the squill, *Urginea Maritima.* Skin testing in their patient was reported as negative.

In our patient sensitivity was acquired from tincture of digitalis. Digitoxin, a crystalline derivative of whole leaf likewise gave manifestations of systemic reaction when given orally or when injected into the skin. In so far as we can determine, there are no previous reports of digitalis sensitivity associated with positive skin tests. The skin reactions were elicited regularly only with the pure glycosides. While the whole leaf itself failed to demonstrate specific antibody convincingly, serum from a patient saturated with the whole leaf did react directly and by passive transfer. It might be inferred that there is conjugation of some fraction of the drug with a body protein which is the specific complete antigen, and this explains the failure to demonstrate reagin for the whole leaf with the same preciseness as that for substances derived from it. The three- to five-day incubation period from the time of administration, either by ingestion or when injected into the skin, to the period of systemic reactivity might also be explained on this basis.

SUMMARY

A case of allergy to digitalis is presented which reacted with a severe urticarial response, and which demonstrated specific skin-sensitizing antibody to digitalis glycosides.

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Editorial

ALLERGY TESTING LABORATORIES

THE usually conservative New York County Medical Society recently shocked several score of its members who are actively engaged in the diagnosis and treatment of allergic diseases by carrying in its official publication, *New York Medicine,* a large advertisement of a commercial laboratory offering complete allergy testing service and the preparation of allergens for treatment. This notice gave no indication whether these services were performed under the supervision of a certified specialist in allergy or even a licensed physician. The merits of this particular laboratory and the wisdom of a county medical society in aiding the promotion of a commercial laboratory in direct competition with its own members, are matters for local concern. However, the advertisement is of general interest as a reminder that commercial laboratories are still actively engaged in the practice of allergy and publicizing their services by various forms of advertisement not available to the ethical practitioner.

This type of laboratory is not new. A number of laboratories have offered allergy skin testing service for years, but in most cases the quality of their work has not inspired confidence and one is surprised that general practitioners continue to refer patients to them. The establishment of certification of specialists in allergy indicates the belief of representative national medical organizations that the diagnosis and treatment of allergic diseases is a field of medicine requiring special training and skill, rather than a function of a laboratory technician. Whether or not he meets the standards of the boards of certification fully, the well-trained physician specializing in allergy is able to offer a type of service beyond the scope of any laboratory, and it is to the best interest of the patient that such service is rendered. Allergy skin tests, even in the best hands, entail a certain risk of severe or even fatal reaction, but this risk is greatly lessened when the tests are performed by a person who adequately understands the patient's history and general physical condition. Even more important is the need of such knowledge for the intelligent interpretation of the results of the tests. Diagnosis based on the blind acceptance of slight or questionable reactions to skin tests, rather than a careful appraisal of the patient as a whole, also leads to futile therapy, such as the treatment of purely infective asthma with injections of house dust or dietary restrictions. Even patients with tumors of the bronchi may lose valuable time while being subjected to such treatment.

To some extent, local custom and personal knowledge of each others' capabilities and interest will influence the division of responsibility between the allergist and the physicians referring patients to him, but in the long run,

what is expected of the allergist will depend on the services he has rendered in other cases. If he gives each patient the careful and comprehensive appraisal that should be expected of a physician with special knowledge of the disease he will soon be recognized as a valuable consultant. On the other hand, if he or his assistant simply performs a routine series of skin tests and reports the results, he is actually performing as a technician, and it is not surprising if the general practitioner feels that a commercial laboratory could fulfill the same function. It is the possession and use of sound judgment that make a good allergist, not the possession and use of a set of diagnostic allergens.

Announcements

FOREIGN ALLERGY MEETINGS

Brazil

Word has been received that the Second International Congress of Allergy in Rio de Janeiro, under the auspices of the International Association of Allergology, will probably be held during the first week of November, 1955.

Finland

The Finnish Allergy Society meets three or four times a year. At its meeting on April 28, 1954, Prof. Nilzen of Stockholm, as their guest, spoke on The Influence of the Thyroid Gland on Experimental Allergic Reactions.

President:	Dr. Zaida Eriksson-Lihr,
	Kammionk 9 B, Helsinki
Vice-President:	Dr. Veikko Pirilä
Treasurer:	Dr. Rita Wangel
Secretary:	Dr. Ossi Pettay

France

La Société Française d'Allergie holds three meetings a year, on the third Tuesday in the months of February, June, and November. The meeting of June 15, 1954, was held at the Faculty of Medicine of Paris.

President:	Dr. Edwin Sidi
Secretary General:	Dr. P. Blamoutier
	5 rue de Luynes, Paris VII

Great Britain

The British Association of Allergists will meet in Leicester, England, on July 3, 1954. Dr. Leslie N. Gay of Johns Hopkins University will present a paper on The Treatment of the Ambulatory Asthmatic with ACTH.

President:	Dr. R. S. Bruce Pearson
Vice-President:	Dr. David A. Williams
Treasurer:	Dr. C. J. C. Britton
Secretary:	Dr. A. W. Frankland,
	Wright-Fleming Institute of Microbiology,
	St. Mary's Hospital Medical School,
	Paddington, London W. 2

Italy

La Associazione Italiana per lo Studio di Allergia will hold its next National Congress in December, 1954, either in Naples or in Rome. The exact date has not yet been announced.

Hon. President:	Prof. Cesare Frugoni
President:	Prof. Antonio Lunedei
Secretary:	Dr. Umberto Serafini
	Via Giucciardini 2, Florence

Mexico

La Sociedad Mexicana de Allergistas held its Eighth Reunion at San Miguel Regla, Mexico City, on Feb. 5, 6, and 7, 1954. A number of Fellows of the Academy presented papers as guests of the society.

Netherlands

The Nederlandse Vereniging voor Allergie held its first meeting of the year on May 8, 1954, the principal topic being Hay Fever. Its second meeting was held on June 19, 1954, at Amsterdam.

Vice-President: Prof. Prakken
Treasurer: Dr. C. Lind von Wijngaarden
Secretary: Dr. W. J. Quarles van Ufford
Emmalaan 17, Utrecht

On May 7, 1954, the day preceding the first meeting, Dr. Willem F. Kremer of Amsterdam died after a long illness. Dr. Kremer had been President of the Society since its founding. He was elected a Fellow of the Academy in 1947 and presented a paper before the Annual Meeting of the Academy in Los Angeles in March, 1950.

Norway

The Norwegian Society of Allergy met on May 13, 1954. At this meeting, Dr. Olav Refvem presented a paper on Sarcoid Tissue as a Hypersensitivity Reaction.

Chairman: Dr. Niels Danbolt
Vice Chairman: Dr. Michael Kobro
Secretary: Dr. Oddvar Andrup
Department of Dermatology
University Hospital, Oslo

The Northern Society for Allergological Research will hold its next Congress in Oslo on Sept. 9, 10, and 11, 1954.

Republic of the Philippine Islands

There is no allergy society of the Philippine Islands, as Dr. Arturo Rotor, Acting Dean of the Medical School, University of the Philippine Islands, and Lt. Col. Conrado B. Icasiano, M.D., of the Philippine Army are the only two physicians in the Islands who are devoting a large part of their practice to allergy. Dr. Rotor was elected a Member of the Academy in 1945. Dr. Icasiano was elected a Member in 1954. Dr. Rotor writes that he expects the situation will improve as more men receive training in allergy. He requests information on residencies in allergy in the United States.

Spain

La Sociedad Espanol de Alergia held its Third Annual Congress in January, 1954, in the Canary Islands.

Switzerland

The Swiss Allergy Society held its annual meeting in Zurich on May 20, 1954.

President: Prof. W. Jadassohn
Secretary: Dr. J. Mozer

The morning session was given over to the subject of Cortisone and Infectious Diseases. The afternoon session was devoted to the presentation of shorter reports on a number of subjects.

Howard Osgood

Course in Pediatric Allergy

The New York Medical College, Flower and Fifth Avenue Hospitals, Division of Graduate Studies, announces a Post Graduate Course in Pediatric Allergy, under the direction of Bret Ratner, M.D., Professor of Clinical Pediatrics and Associate Professor of Immunology, Nov. 3, 1954, to May 25, 1955, 30 sessions, Wednesdays, 9 A.M. to 4 P.M. The fee will be $300.00. The course consists of lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds, and animal experimentation covering basic principles of diagnosis and treatment of allergy in children, and applied immunology. Applicants

must be certified in pediatrics or have the requirements for certification. Enrollment is limited. Apply to the Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, N. Y. A research fellowship in Pediatric Allergy is also available. Application for the latter should be made now.

COURSE IN ALLERGIC DISEASES

The Faculty of Medicine of the University of Paris announces a course in allergic diseases under the direction of Professor Pasteur Vallery-Radot, to be held at the Clinque Medicale propedeutique de l'Hôpital Broussais, 96, rue Didot, Paris XIV^{e}, from Oct. 18 to 28, 1954.

The course will comprise theoretical instruction and practical demonstration, by Professor Vallery-Radot, Dr. Halpern, and associates. The fee is 5,000 francs for the didactic teaching and 8,000 francs for the didactic and practical portions.

Book Review

Fabismo y Hemolisis Alimentaria. By R. Surinyach, with the collaboration of F. Marcolongo, Barcelona, Spain, S. Alcobe and C. A. Llebaria, 1953; IV Congreso Internacional de Higiene y Medicina Mediterraneas.

In this report presented by Dr. R. Surinyach (Barcelona) to the Fourth International Congress of Mediterranean Hygiene and Medicine, the chapter on the Pathogenesis of the Syndrome has been written by Professor F. Marcolongo (Cagliari, Italy), that on Genetics by Professor S. Alcobe (Barcelona), and the chapter on Hematology by Dr. C. A. Llebaria (Barcelona). In spite of the fact that the paper is presented in a systematic form for the better description of the disease, the authors express their points of view with absolute independence.

Favism is an acute hemolysis with hemoglobinuria brought about by the ingestion of fava beans, the edible seed of the *Vicia faba*. The term "alimentary hemolysis" is used to include the whole group of similar hemolyses provoked by the ingestion of a number of foods which are harmless to the majority of individuals. Favism constitutes the best known form of alimentary hemolysis.

While the allergic nature of favism has never been established and the present work lends it little support, the suspicion that an antibody mechanism may play a part in its pathogenesis has attracted the attention of allergists to the condition and the present review which is published in Spanish includes a nine-page summary in English, which may be of interest.

The condition occurs particularly in Sardinia and Minorca, but other foci occur throughout the Mediterranean area.

Twelve cases have been described in the United States and one in the Argentine Republic in immigrants or descendants of immigrants from Mediterranean countries.

The seasonal incidence of favism coincides with the periods of collection and consumption of fresh fava beans. The pathogenic activity of the fava bean increases in certain years, producing an increase in the number of patients.

There are certain clinical forms provoked by inhalation when the patient approaches a plantation of fava beans. According to the author's experience, the crises of favism produced by inhalation always take place in individuals who are susceptible to suffering favism by ingestion, but the reverse is not always true.

The cases of inhalation-favism have been considered to be produced by pollen, a hypothesis which is interdependent with the allergic theory of the disease. The author (Surinyach) observed that in the great majority of his cases affected with inhalation favism, it was possible to exclude the pollen as the causative factor. This was demonstrated by the aerobiologic studies and by the clinical circumstances of the majority of cases, viz.: the appearance of symptoms proved by: (1) the approach to the plants not in the flowering period, (2) the shelling of the fava beans or the culinary preparation of the same, etc.

After this demonstration, the factor or agent inhaled is considered to be the volatile oil or osmyls of the *Vicia faba*. According to present knowledge, the toxicity of ingested beans may be related to the existence of plant agglutinins and analogous substances present in the plants known to be causative of the Alimentary Hemolytic Syndrome.

Marcolongo considers that the pathogenesis of icterohemoglobinuric favism is very complex and not altogether well understood, in spite of the fact that considerable progress has been obtained in the last years.

Heredity appears to play a part in predisposition to the disease.

Surinyach describes the clinical picture of an attack of alimentary favism of moderate severity. About three hours after the ingestion of fava beans, and generally before the lapse of twenty-four, the clinical picture is ushered in by general malaise, nausea, vomiting, headache, stupor, and fever. After a short interval of time, hemoglobinuria and jaundice make their appearance. The temperature is generally mild and ends by lysis. The hemoglobinuria and jaundice usually last for three to four days, and both are accompanied by albuminuria. The red cell count is considerably diminished, at times it may reach as low as 800,000 per cubic millimeter or even less. One of the most characteristic features of the disease is the surprisingly rapid clinical recovery which runs parallel with the red cell recuperation curve. Death may occur due to collapse or because of nephritis and uremia during the first days of the disease.

Blood transfusion is the principal form of therapy, but cortisone and corticotrophin are being tried.